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AUSTRALASIAN ANNALS OF MEDICINE

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DYSTROPHIA MYOTONICA AND THE OCCURRENCE OF CONGENITAL PHYSICAL DEFECT IN AFFECTED FAMILIES[1]

J. E. CAUGHEY AND J. BARCLAY[2]
New Zealand

IN previous studies of families with *dystrophia myotonica* in New Zealand, Caughey and Brown (1950) gave an account of some endocrine aspects of the disorder, and Caughey and Gray (1954) described radiological changes in the skull and unilateral elevation of the diaphragm. The present study deals with some of the families previously reported and others since studied. Attention is drawn to certain hereditary aspects of the disorder, and in particular to the incidence of congenital physical defects, which occur in the children of the so-called "dystrophic" generation and less frequently in the "dystrophic" generation itself.

Previous authors have stressed the incidence of mental defect (Batten and Gibb, 1909; Ravin and Waring, 1939; Maas and Paterson, 1937; Maas, 1937; Maas and Paterson, 1943). Others have reported a high incidence of miscarriages and stillbirths and a high infantile mortality (Batten and Gibb, 1909; Fleischer, 1918; Maas, 1937; Maas and Paterson, 1943; Thomasen, 1948). Our own records support these opinions; but in addition we have encountered a high incidence of congenital physical defects in the families. In view of the incidence of miscarriages, stillbirths and congenital mental defects, it might have been predicted that these would occur; but in the literature we find no general recognition of them.

Our own cases have occurred in 17 families with *dystrophia myotonica* encountered in New Zealand in the past seven years. In all there have been 40 patients with the fully developed disorder in the Auckland and Dunedin areas with a population of 424,550. In none of the families was there any reasonable doubt as to the diagnosis of *dystrophia myotonica*, but a brief description will be given of the presenting member of each family in order that the diagnosis may be quite apparent.

FAMILY RECORDS

Family I: H. (Figure I)

III, 1.—The presenting patient was R.F.H., aged forty-two years, a retired farmer. On joining the forces in 1941 he had noticed difficulty in relaxing his grip while doing rifle drill. Since that time he had

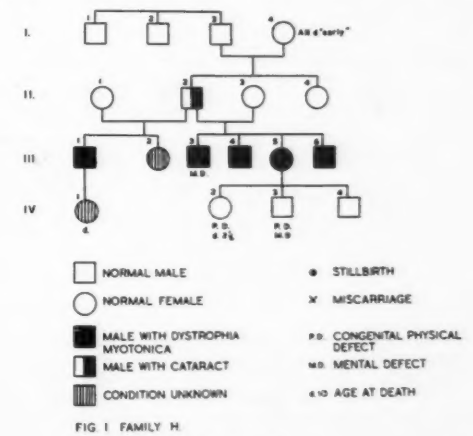

FIG. I. FAMILY H.

FIGURE I

noticed weakness and wasting in his neck, forearms and legs. For four years there had been loss of potentia. He had a myopathic facies and frontal baldness. There was active myotonia of the grasp and mechanical myotonia of the tongue and the thenar eminences. Marked wasting and weakness of the

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anterior cervical muscles, of the flexors of the trunk and of the muscles of the forearms and legs were present. He had bilateral lenticular opacities and the testes were small and soft.

It will be seen from Figure I that one female (III, 5) with the fully developed disorder had three children, two of whom had congenital physical defects.

IV, 2.—This female child, now deceased, was not examined by us, but we have a clinical photograph provided by Dr. C. Pickerill, to whom we are indebted. The child was born with a cleft palate and hare-lip, and as far as we can ascertain had no evidence of myotonia or wasting. At two and a half years she died of tuberculous meningitis.

IV, 3.—J.H., a male patient, was aged eleven years. This boy at nine years had presented a difficult problem of management. He frequently wandered away from home for long periods and subsequently was taken in acts of theft and juvenile delinquency and was committed to the Otekaike Special School for boys. When examined he was alert and co-operative, but he was reported by his school teacher as being backward in school. His intelligence quotient was 88 and he was classified as a high grade imbecile. There was a large cleft in the palate anteriorly just posterior to the left upper incisor and extending up to the nasal fossæ. The uvula had a median shallow groove or cleft and there was a hare-lip. The sterno-mastoid muscles were well developed. There was no active or mechanical myotonia.

Family II : M. (Figure II)

II, 4.—The presenting patient was F.M., a male pensioner, aged forty-five years. When aged twenty-seven years, he had noticed increasing weakness and wasting of the neck, arms and legs. Three years later he noticed difficulty in relaxing his grasp and his

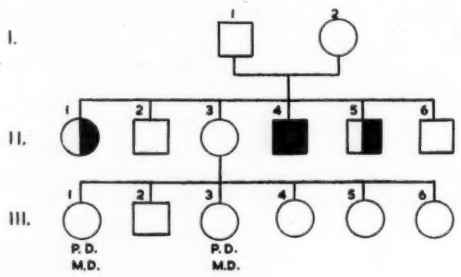

FIG. 2 FAMILY M.

FIGURE II

visual acuity deteriorated. Bilateral cataracts were enucleated subsequently. He had failure of potentia and libido. He had a myopathic facies with weakness of lid closure. He had considerable weakness and wasting of the anterior cervical muscles and of the forearm and the leg muscles. He was unable to raise his head off the pillow or to sit up when his arms were folded across his chest. His grasp was myotonic and there was mechanical myotonia of his tongue and thenar eminences. His gonads were soft and small. X-ray examination of the skull revealed *hyperostosis frontalis*.

III, 1.—E.P., aged twenty-two years, had spastic paraplegia. She was a dull girl attending a school for backward children. She had had difficulty in walking since childhood. She had a severe degree of myopia and her speech was halting. Her left hand was smaller than the right, and there was wasting of the thenar muscles of the right hand. The tone, power and co-ordination of the upper limbs were normal. The deep reflexes were increased. The abdominal reflexes were not obtained. The lower limbs were spastic, the left more than the right. The deep reflexes were exaggerated and the left plantar response was extensor in type, the right flexor. There was no evidence of wasting or myotonia.

III, 3.—L.P., aged nineteen years, had spastic paraplegia. She was reported to have been normal at birth, but at fourteen months was diagnosed as suffering from cerebral palsy with paraplegia. At three years she was unable to walk and she was backward in her speech. She had a severe visual defect and spontaneous nystagmus. She was treated at a home for " spastics " until the age of five and a half years, but she was unable to go to school on account of the speech defect and the difficulty in walking. She was dull and backward. Her mental age was eight years. She walked with great difficulty and had to hold on to any support within reach. The upper limbs were not wasted and the tone, power and coordination were normal. The deep reflexes were brisk and equal. The abdominal reflexes were not obtained. The lower extremities were spastic, adducted and partially flexed at the hips and knees. The muscles of the right thigh were hypertrophic. The deep reflexes were greatly increased. There was bilateral ankle and patella clonus and the plantar reflexes were extensor in type. There was no evidence of myotonia. The visual defect was due to a compound myopic astigmatism. There was no evidence of cataract. Her speech was slurred and unintelligible. Emotionally she was euphoric and facile.

Family III : L. (Figure III)

III, 3.—The presenting patient was Mrs. M.M.L., aged thirty-three years. Seven years earlier she had noticed difficulty in relaxing her grasp, which was first apparent when she was milking. Also she had difficulty in opening her eyes if she was awakened suddenly in

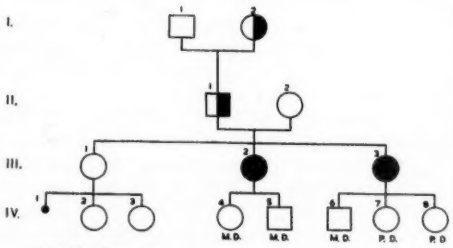

FIG. 3 FAMILY L.

FIGURE III

the night. She developed a tendency to fall on unexpected occasions. She had a myopathic facies with weak lid closure, and her speech was dysarthric. The anterior neck muscles were wasted and weak, and there were wasting and weakness of her forearms, abdominal muscles and legs. There was pronounced active myotonia of the grasp and mechanical myotonia of the tongue. Bilateral lenticular opacities were present. Mentally she was retarded.

IV, 6.—L., a male subject, aged seven years, appeared to be normal at birth, but was retarded in his speech and could not talk until the age of three years. His mother reported that he was making quite good progress at school. He was one year behind his age group at school.

IV, 7.—M.L., a female subject, aged three years, was born at full term. Her mother stated that her own health had been good throughout pregnancy, there being no history of rubella or other infective

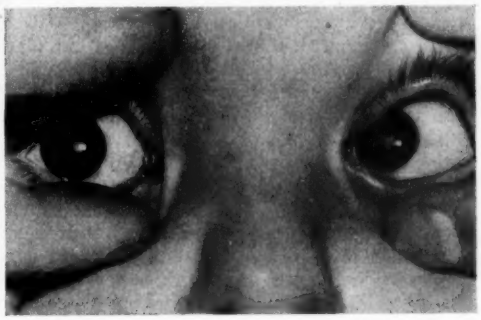

FIGURE IV

illness in the critical early weeks of pregnancy. The child was blind from birth on account of bilateral dense white congenital cataracts (Figure IV). Nystagmus and an internal strabismus of the left eye were present. There was no evidence of muscle wasting or myotonia.

IV, 8.—H.L. was a female subject, aged fourteen months. There was no history of maternal illness during pregnancy, and she was delivered by Cæsarean section. She had congenital bilateral *talipes equino-varus*. She was backward in her speech, but otherwise was apparently normal.

were wasting and weakness of the forearms and legs, and no deep reflexes were obtained. There was mechanical myotonia of the tongue and of the thenar and hypothenar muscles of both hands. Pronounced active myotonia of the grip was present. He had paralysis of the right vocal cord.

II, 14.—R.S. was aged forty years. Since birth his legs had been stiff and he had had constant difficulty with walking and had not learned to walk normally. He had used two walking sticks until eight years previously and then began using crutches. For two years he had had some urgency of micturition and some incontinence of urine. He was euphoric and had some hypochondriacal ideas, and mentally he was dull. The cranial nerves were normal. There were no lenticular opacities. The upper extremities were well developed and the tone was moderately increased. The deep reflexes were increased and the abdominal reflexes were present. The lower limbs were well developed, well nourished, hypertonic and in a state of adduction spasm. There was severe paresis of both lower limbs, there being no movement at the ankles and little at the knees and hips. Adduction could be overcome only by flexion at the hip joints. The deep reflexes were exaggerated and the plantar responses were extensor in type. On painful stimulation of the soles of the feet a flexor spasm was induced. There were some contractures of both feet. There was no evidence of active or mechanical myotonia and no wasting of the neck, forearms or legs. He had an intelligence quotient of 80 and a mental age of eleven to twelve years.

Family V: C. (Figure VI)

II, 2.—The presenting patient was Mrs. C., a housewife, aged thirty-two years. After the birth of her last child twelve years previously, she had noticed increasing fatigue and debility. Over the same period she had noticed inability to relax her grasp and progressive weakness of her arms and legs, and at the time of examination she was unable to walk more than a few hundred yards. She had had six miscarriages. She had a myopathic facies with bilateral ptosis and weakness of all the muscles of expression.

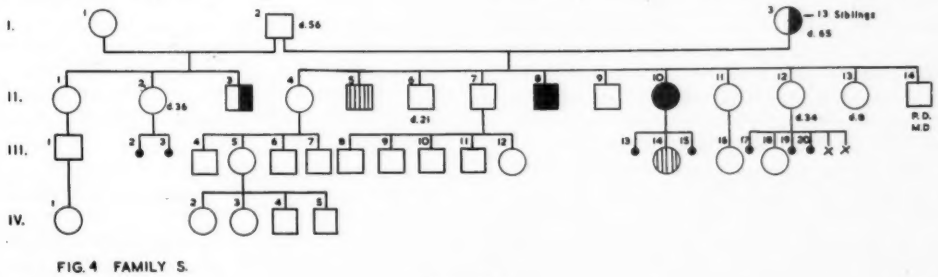

FIG. 4 FAMILY S.

FIGURE V

Family IV: S. (Figure V)

II, 8.—The presenting patient was P.S., a male pensioner, aged fifty years. Twenty years earlier he had first noticed difficulty in relaxing his grip; six years earlier his vision began to fail, he became weak and the muscles wasted in his neck, arms and legs. His speech became slurred. He had bilateral cataract, a myopathic facies, and wasting of the sterno-mastoids and other anterior cervical muscles. There

Lid closure was weak. There was mechanical myotonia of the tongue, thenar and hypothenar eminences, and the grip was myotonic. The anterior cervical muscles were wasted and weak, as were the forearms and legs.

In both lenses, cataracts characteristic of *dystrophia myotonica* were present. There were multiple pigmented moles over the limbs and trunk. The radiograph of the skull showed a very small pituitary fossa with thickening of the calvarium, *hyperostosis frontalis* and extensive pneumatization of the sinus areas.

III, 4.—This subject was a schoolboy, aged twelve years. During a routine physical examination for poliomyelitis he was discovered to have *dystrophia myotonica*. He was born prematurely and had bilateral congenital inguinal herniæ and also congenital *talipes equino-varus*. The herniæ were repaired in 1941 and he had an orthopædic operation for the talipes in 1945. At school he was backward and mentally dull, being five years behind his age group. He was a poorly developed youth with a myopathic facies and weakness of lid closure. He had bilateral myotonia of the grip and mechanical myotonia of the tongue and thenar muscles. The anterior cervical muscles, the abdominal muscles and the muscles of the forearms and legs were weak, but not obviously wasted.

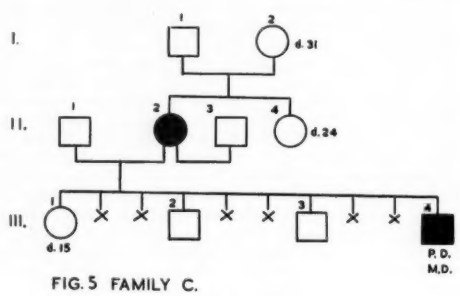

FIG. 5 FAMILY C.

FIGURE VI

DISCUSSION

Adie and Greenfield (1923) state that stigmata of degeneration may often be present in families with *dystrophia myotonica* and comment on the frequency with which a very high, narrow palate is observed in these patients. Other writers have noted the association of this type of palate with the disease, and in Katzenstein-Sutro's (1938) family of 122 members, of whom seven were affected with *dystrophia myotonica*, 11 had a high arched palate and 21 had bad or anomalous or ill-placed teeth. Some observers would be unwilling to subscribe to the suggestion that a high arched palate could be regarded as evidence of congenital physical defect.

Bramwell (1923) states that there is a relative frequency of congenital stigmata of various kinds in *dystrophia myotonica*, in which respect the disease differs from the other myopathies, in which there appears to be a tendency to congenital muscle defects but not to other congenital stigmata. Ravin and Waring (1939) are of the opinion that *dystrophia myotonica* belongs to the group of heredofamilial degenerative diseases. Families in which such degenerative diseases occur have been thought to show degenerative stigmata such as mental or physical inferiority in members not affected by the disease. They quote Henke and Seeger (1927) who, after comparing the number of such stigmata in a family in which *dystrophia myotonica* was traced through several generations with the incidence in a comparable normal family, came to the conclusion that the incidence of these conditions was not increased in the *dystrophia myotonica* family, and that these conditions had nothing to do with the *Anlage* for *dystrophia myotonica*.

Herner (1940) records only one case of congenital physical defect in a member of the fifth generation. This member, who was the offspring of an apparently normal parent, had bilateral talipes, was mentally defective and developed *dystrophia myotonica* at puberty. Bell (1947), in her comprehensive investigation of the hereditary aspect of the disease, does not discuss the incidence of congenital deformities; but some interesting examples are to be found in the pedigrees recorded at the end of the monograph. These pedigrees are of patients and their families investigated by Maas and others. One mother with the fully developed disease had five children, of whom the eldest died in infancy, the second, who was backward at school, developed *dystrophia myotonica*, and the youngest was mentally defective and had myotonia. The remaining two, as well as having widespread muscular wasting, were microcephalic idiots, one of whom had congenital heart disease and the other undescended testes.

In another family, a male with myotonia and cataract had six children, of whom the first and fourth died in infancy and the youngest had congenital absence of the right *pectoralis major* muscle. A mildly affected mother had four children, the youngest of whom had *spina bifida* as well as mental defect and myotonia. A severely affected father, who had a congenital anomaly of the eyelids, had one mildly affected son who was a deaf mute and also had an eyelid anomaly similar to that of the father.

In Katzenstein-Sutro's (1938) family, one member and his grandson had undescended testes.

In Kryschowa and Bajevskaja's (1934) family, the nine children of a woman with presenile cataract in the second generation show some interesting features. The second child had bilateral cataract, a shortened *ligamentum nuchæ*, and an accessory nipple in the pubic region. He also had kyphoscoliosis and atrophy of his scapular muscles. This member had four apparently healthy children; but one grand-daughter had bilateral epicanthus, *pes cavus* and syndactyly between the second and third toes. The third child had a cataract in

the left eye, shortening of the *ligamentum nuchæ*, asymmetry of the face and *pes cavus*. The fourth child had a shortened *ligamentum nuchæ*, scoliosis and *pes cavus*. His son had facial asymmetry and epicanthus on the left side.

In a family with cataract and *dystrophia myotonica* investigated by Voss (1938), two of the offspring of apparently normal parents in the third generation had microphthalmos and colobomata of the iris and choroid, bilateral in one case and unilateral in the other.

Fleischer (1918) described one case of imbecility associated with muscular atrophy and deformity of the hands and feet among the nine offspring of a mentally defective father with cataract.

Baake and Voss (1917) describe a family in which there was no abnormality until the third generation, when in a family of nine offspring the first showed *dystrophia myotonica*, the second, third, fourth, fifth and eighth were normal, the seventh was an idiot, and the ninth was mentally defective. The sixth child was a high-grade mental defective with talipes, paralysis of the legs and involvement of his sphincters.

Boeters (1935) describes a family, a number of whom showed dystrophic or endocrine abnormalities with or without myotonia. Few details are given of the nature of the abnormalities or the time of onset, but three members are stated to have had enuresis, one was born prematurely and mal-developed, two had strabismus, five were left-handed, and one had spastic paraplegia.

In a family first investigated by Greenfield and later by Maas, one member of the fifth generation, the offspring of a normal parent, had a congenitally short right arm and no fingers on the right hand.

One member of Franceschetti's (1942) family had coxalgia on the left side at the age of four years, followed by complete ankylosis of the hip. At twenty years he became aware of weakness in his arms and legs, and at thirty-four years he was incapable of intellectual work. He was bald and obese, his skin was dry, he had a parenchymatous goitre, left labyrinthine deafness, early cataract and undescended testes.

Thomasen (1948) mentioned two cases of congenital physical defect, both in the offspring of an affected parent. One of these, an imbecile with active and mechanical myotonia, had *talipes valgus*; the other, an imbecile, who had to be admitted to a mental hospital at the age of eleven years, had right *talipes calcaneus*, left *talipes equino-varus*, myotonia and wasting.

Greenfield (1911) first drew attention to the association of cataract with *dystrophia myotonica*, and a number of writers have published further records and discussed this feature of the disease. There are numerous examples of the occurrence of cataract in several generations of affected families and in the offspring of parents with *dystrophia myotonica*. Gifford, Bennett and Fairchild (1929) state that apart from a few cases in which optic atrophy has been seen, no involvement of the eye except cataract seems to occur. Only two cases of congenital cataract were found in the literature, and both of these were in the pedigrees at the end of Bell's (1947) monograph. In one branch of the family described by Greenfield and later by Maas, cataract was the main symptom to be found. A mother with cataract had three offspring with cataract and one with glaucoma. One of the offspring with cataract had a mentally defective child with congenital cataract. No muscle symptoms were found in these members. Another case occurred in one of Maas's families, in which one of the seven offspring from an affected mother was mentally backward and had left-sided congenital cataract.

In a previous publication (Caughey and Gray, 1954) an account is given of three patients with *dystrophia myotonica* who had unilateral elevation of the diaphragm. It is pointed out that the nature of the diaphragmatic lesion is obscure, but it is possible that it is due to a congenital physical defect.

From the foregoing scattered examples of congenital physical defect which have been found in the literature and from our own studies, we are of the opinion that such defects should be accepted as one of the variable features of disease occurring in families afflicted with *dystrophia myotonica*. It may occur in the "dystrophic generation" with or without the fully developed disease picture and with or without associated mental defect. It is more likely to present in offspring of the "dystrophic generation", and often occurs with mental defect. From our own studies it seems probable that affected women of the "dystrophic generation" are especially liable to have children with some congenital physical defect.

Following Greenfield's (1911) paper it was established that cataract was one of the variable features of the disease both in the "first" generation, when it occurs as a senile or presenile cataract, and in the dystrophic generation. There has been no recognition of congenital cataract in the disease picture. From our own experience and from the cases gathered from the

literature we believe cataract of a congenital type will probably come to be accepted as one of the variable features of the disease in these families, and it probably differs in form from the more characteristic type seen in *dystrophic myotonica*.

Although there is a high incidence of congenital physical defect in the members of the families which we have investigated, we are not able so far to draw any statistical conclusions from our findings. Our total number of patients investigated is relatively small, and we have not determined the incidence of similar defects occurring in comparable normal families. Furthermore we are unable to find any statistics showing the incidence of similar congenital defects in the general population.

SUMMARY

An account is given of 10 patients with congenital defects occurring in five families afflicted with *dystrophia myotonica*. The conditions include all grades of mental defect, congenital cataract, hare-lip and cleft palate, talipes, spastic paraplegia, herniæ and syndactyly.

These defects may occur in the " dystrophic generation ", but are more likely to occur in the children of the " dystrophic generation ".

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INVESTIGATIONS OF MUSCULAR WEAKNESS IN MIDDLE LIFE: THE SO-CALLED MENOPAUSAL MUSCULAR DYSTROPHY[1]

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THE term menopausal muscular dystrophy was first used by McEachern (1951) to describe a type of myopathy which occurs predominantly in women at or after the menopause. The condition was recognized by Nevin in 1936, who described two cases of " muscular degeneration occurring in late adult life ". The clinical reports of these two cases leave no doubt that the disease so described was identical with that described by McEachern. Briefly the disorder is a dystrophy involving the large proximal muscles of the extremities. The first symptoms are referable to the legs, and consist of difficulty in mounting stairs or in getting out of chairs. These early symptoms are followed by difficulty in walking more than a short distance, and by unavoidable and unpredictable falls with subsequent difficulty in regaining the erect posture. The onset may be sudden or gradual, but in most cases it has been present for some years before recognition. Weakness which is symmetrical is progressive for a number of months or years, whereafter it remains stationary or progresses very slowly. In the lower extremities, the muscles most affected are the iliopsoas, the glutei, the *quadriceps femoris* and the adductors, whilst in the upper extremities the deltoid, biceps, brachialis, triceps, *serratus anterior*, supraspinatus and infraspinatus are the muscles most usually involved. The muscles of the forearm and the leg below the knee are rarely involved. There is little if any wasting of the involved muscles. The deep reflexes remain, and there are no signs of involvement of the central nervous system. Because the disorder is not as yet widely recognized, the diagnosis has seldom been made, symptoms being regarded as constitutional or attributable to obesity, to hysterical weakness or to the enfeeblement of age. However, the condition can be diagnosed readily by clinical examination and can be confirmed by electromyography or muscle biopsy, or both. The electromyogram is characteristic of the changes found in muscular dystrophy, and the histopathological changes are distinct from those of the well-recognized juvenile form of dystrophy (Shy and McEachern, 1951).

In this paper are reported a further six cases of the syndrome, together with electromyographic assessment of response to tocopherols in four and cortisone in two. Case I presents the usual clinical picture and is presented in some detail. Case II is unusual, in that the onset occurred four years before the menopause. Case III is that of a male suffering from the disease. Case IV appears to differ basically from the others. The onset was relatively acute, with pain in the affected muscles; there was transient affection of deglutition, a rash was present, and recovery of strength was considerable. The picture is that of acute polymyositis rather than of dystrophy. Cases V and VI present no unusual features and are reported briefly.

CASE REPORTS

CASE I.—Miss M.E.M., a trained nurse, aged sixty-five years, was admitted to the Royal Adelaide Hospital in February, 1952, with a thrombosis of the right femoral vein, which developed without obvious precipitating cause. After two weeks she was discharged from hospital, but was readmitted three days later with a large pulmonary embolism, which was successfully treated with heparin and dicoumarol. Whilst she was convalescing, it was noted that the gait was " waddling ". Further investigation of her history revealed that some five years earlier she had developed difficulty in getting her bicycle in motion, but once it was under way there was no further trouble. Because of falls when mounting the bicycle she sold it and took to travelling by tramcar. Her transport problem was not solved, however, because she had to hoist herself up with both arms, a difficult situation arising when there were parcels to carry. From the onset of muscular weakness she noted a progressive decrease in the distance she was capable of walking, and by the time of her admission to hospital she could manage only one city block, and that with difficulty and with the aid of a walking stick. She continued with her vocation as a nurse in private homes only on the understanding that she be permitted to sit down for a quarter of an hour after each hour's work. Sudden

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and unpredictable falls occurred so frequently that she had learnt to fall without injuring herself. From these falls she was unable to get up without assisting herself by pressing the hands on the thighs. Most of her dresses were threadbare on the right thigh, from a habit of frequently supporting herself by downward pressure of the right hand on the right thigh. Over the preceding two years she had found difficulty in keeping the arms elevated, and was accustomed to dressing her hair whilst lying on her bed with a pillow under the small of the back.

On examination of the patient, she was overweight and elderly. She was able to walk a few paces only, and the gait was waddling because of the alternating downward fall of the pelvis to the side of the leg being brought forward. This, presumably, resulted from weakness of the *gluteus medius*. In recumbency she was barely able to raise the extended leg. There was weakness of all muscles of the pelvic girdle, and extension of the leg at the knee could be overcome by pressing the foot down with two fingers. There was weakness of all muscles of the shoulder girdle, particularly of the deltoids, the biceps and triceps. The blood pressure was 150 millimetres of mercury, systolic and 80 millimetres, diastolic.

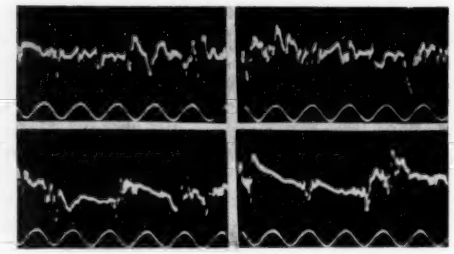

FIGURE I

Electromyograph for Case I, demonstrating the shortened duration of action potentials. Time marker, 50 cycles per second

The volume of urine passed in a twenty-four-hour period was 1640 millilitres, and this contained 125 milligrammes of creatine and 780 milligrammes of creatinine.

In the electromyographic examination the right *gluteus maximus* and *vastus medialis* muscles were explored with a concentric needle electrode. No fibrillation potentials were seen at rest in either muscle. During voluntary effort the number of units recruited appeared normal in both muscles, but many were shortened in duration to only two or three milliseconds (Figure I). Virtually all units with a duration longer than six milliseconds were highly polyphasic. Histograms of the action potential duration in 60 different motor units in the *vastus medialis*, and of a normal muscle for comparison are shown in Figure II.

A biopsy of the right *vastus medialis* was taken. Examination of the section revealed relatively large patches of hyaline necrosis (Figure III). In the areas of healthier muscle, there were fibres and small groups of fibres showing loss of striation, proliferation and central migration of sarcolemmal nuclei. Some fibres showed longitudinal fragmentation, pallor and vacuolation (Figure IV).

At the end of the convalescence from the pulmonary embolism, this patient had difficulty in getting out of bed. She was just able to walk around the bed, using the latter for support. In June, 1952, treatment was started with 300 milligrammes of mixed tocopherols per day. Within two weeks she was able to walk the length of the ward without a stick. Presumably some of this improvement was due to ordinary recovery of muscle function impaired from disuse.

Thereafter improvement was steadily progressive. An electromyogram on September 19 showed the action potential duration of motor units in both muscles

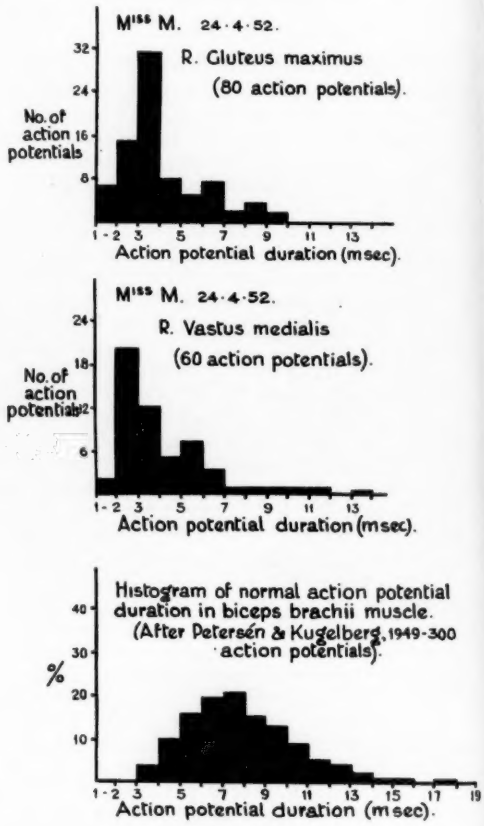

FIGURE II

Histograms of action potential durations obtained from two muscles in Case I. The lowest histogram is from normal muscle for comparison. The shift to the left, indicating shortened duration of action potentials, is seen

to have increased considerably. The right *vastus medialis* muscle had a histogram with a mode in the range five to seven milliseconds, which is almost normal for this type of muscle. A histogram of the action potential duration in 80 different motor units in this muscle is shown in Figure V. The proportion of units in the range two to four milliseconds was still considerably higher than in normal muscle, but appreciable reversion towards normal had occurred since the test on April 24.

By May, 1953, still further improvement had occurred. The patient was working as a nurse in private homes and managing well. The gait was still abnormal in that it was waddling, but she could walk at an average pace with the use of a stick. Thereafter the condition remained stationary. In August, a further electromyogram was not significantly different from that of September 19, 1952. Though by no means relieved of her disability, she considered that she was stronger than she had been before the original illness and the subsequent administration of tocopherols.

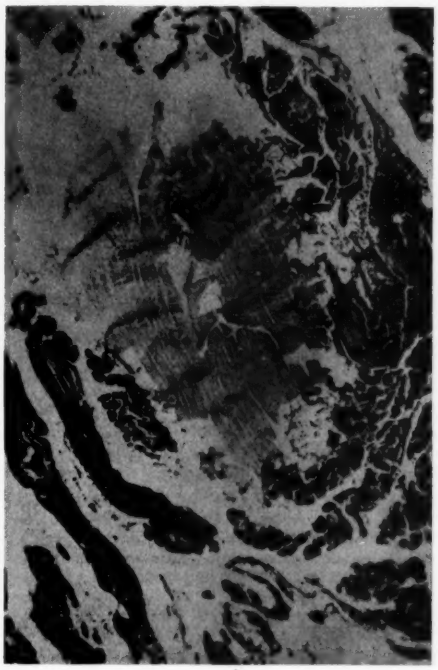

FIGURE III

Muscle biopsy from Case I. A large area of hyaline necrosis is shown in the centre of the field. (×24)

CASE II.—N.I.M.V., aged forty-four years, a married woman with four children, attended the out-patient department of the Royal Adelaide Hospital in April, 1951. She gave a history of muscular weakness present for the preceding seven years. Her attention was drawn to her condition by friends who commented on her "limping" gait. Soon after this she noted difficulty in climbing stairs and had had to pull herself up by the handrail. She then noted that the distance she was able to walk had become considerably less, and when walking she would suddenly fall forward without warning. About five years previously she had noted difficulty in straightening up after stooping, and had developed a rolling gait. Four years previously she had fallen and injured her head and had been subject to occipital headaches subsequently. Weakness of muscles had been very slowly progressive over the last four years. Menstruation had always been regular until it had ceased two years previously.

Examination of the patient revealed that the blood pressure was 200 millimetres of mercury, systolic, and 140 millimetres diastolic; but no other abnormality was detected apart from signs due to muscle weakness. In her walking there was a gross side-to-side throwing of the trunk. This permitted the pelvis to be raised sufficiently to allow the leg to be swung forward. She carried a stick. In order to get up when recumbent she would turn on to her face, slowly and with much difficulty draw up her thighs and then suddenly throw her trunk backwards, push on her thighs with her hands and finally give a jerk to straighten her back and stand upright.

When recumbent she was unable to raise her leg against gravity and to abduct or adduct her thighs, and she could flex her knee to only 90°. Surprisingly,

FIGURE IV

Higher magnification of biopsy from Case I. Across the centre of the field a grossly diseased muscle fibre can be seen. Fragmentation is demonstrated in the middle of the fibre. Loss of striation and increase in sarcolemmal nuclei can be seen. (×210)

extension of the knee was quite strong with good contraction of the quadriceps. All power of movement at the shoulder was reduced, and there was some weakness of flexion and extension at the elbow. The hand grips were strong and she was able to stand on the heels or toes.

Investigations revealed a normal cerebro-spinal fluid containing 40 milligrammes of protein per 100 millilitres. A gruel test meal examination revealed achlorhydria which was not histamine-fast. The result of the Wassermann test was negative in the blood and cerebro-spinal fluid. The basal metabolic rate was +10%. There was no response to 2·5 milligrammes of neostigmine injected intramuscularly. A twenty-four-hour specimen of urine measured 1·7 litres and contained 290 milligrammes *per centum* of creatine and 810 milligrammes *per centum* of creatinine.

Electromyographic study revealed gross abnormality in the left gracilis and *adductor magnus*, the majority of action potential durations being in the two to four milliseconds range (Figure VI). The tracing obtained from the *vastus medialis*, however, showed very little abnormality.

A biopsy specimen was taken from the left *rectus femoris* and later from the *adductor magnus*. In the former very little histological change was detected, whilst in the latter the grossest abnormality of any muscle in the series was found. The greater part of the muscle was replaced by fat, though the framework of the muscle bundle system was still evident. Throughout the section there were scattered islands of muscle tissue, which consisted of short fibres showing total loss of striation, fragmentation and increase of sarcolemmal nuclei (Figure VII).

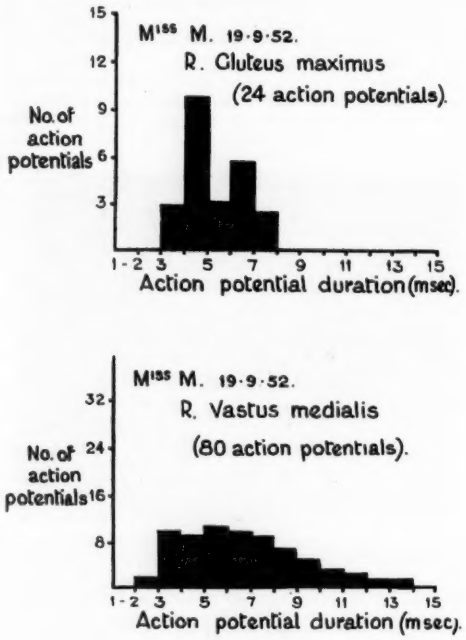

FIGURE V

Case I. Histograms after treatment with mixed tocopherols. Comparison of the lower histogram with the middle one of Figure II shows a pronounced shift to the right

On June 26, 1952, treatment was begun with mixed tocopherols, 150 milligrammes being given daily; this amount was increased to 300 milligrammes daily on September 29. The patient considered that she was walking better since taking tocopherols, but there was no objective improvement. Oral cortisone therapy was initiated on November 6, 1952, in doses of 25 milligrammes every six hours, a total of two grammes being given in the next twenty days. At the end of this treatment she considered that she was weaker. An electromyogram on December 17 showed no significant change.

Tocopherol therapy was resumed but with no appreciable improvement, as might have been anticipated from the histopathological picture of advanced degeneration revealed by biopsy (Figure VII).

CASE III.—C.H., a male shopkeeper, aged sixty-two years, came to the out-patient department in June, 1952, with a diagnosis of progressive muscular atrophy. The history had begun thirteen years previously, when he had suffered an attack of precordial pain which had persisted for two weeks, but which had not interfered

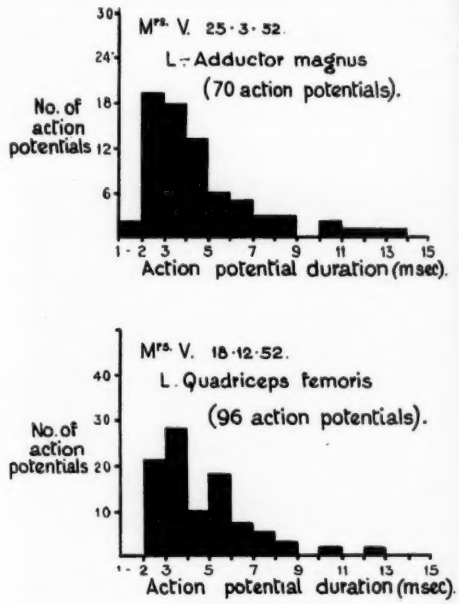

FIGURE VI

Case II. Histograms of action potential duration showing shift to the left

with his occupation. Thereafter he had gradually noticed difficulty in climbing stairs and inability to walk as far as formerly. He had begun using a walking

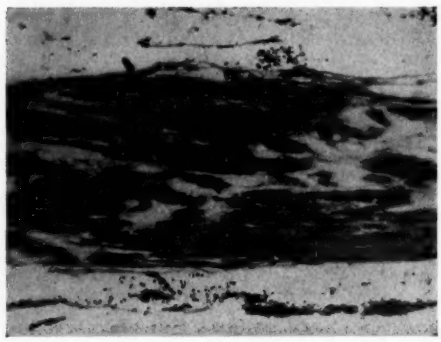

FIGURE VII

Case II. Biopsy of muscle showing gross degenerative changes. (×100)

stick nine years previously, at which time he was forced to abandon his hobby of playing in a band because he could not keep abreast of his fellows when

marching. This weakness was soon followed by weakness of the arms. Weakness had grown progressively worse until two years prior to examination, since when it had remained stationary. At the time of examination he was barely able to walk 50 yards, but was still able to drive a motor-car. There had been no loss of libido and no impotence. Apart from muscular weakness he felt well.

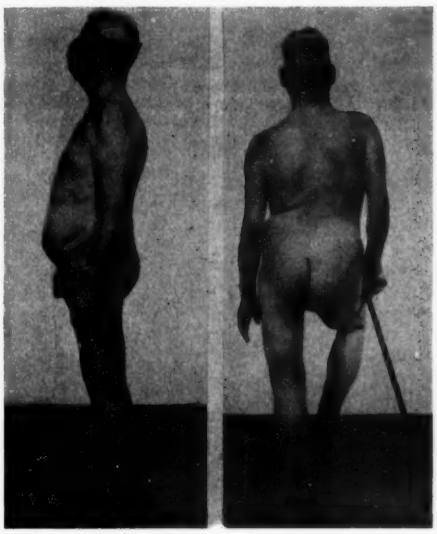

FIGURE VIII

Case III (the only male patient in the series). Muscle weakness was present for thirteen years. Absence of wasting is notable. The figure on the left demonstrates the erect posture and that on the right the tilt of the pelvis in walking, leading to the characteristic "waddling" gait

General medical examination revealed no abnormality except for a blood pressure of 200 millimetres of mercury, systolic, and 115 millimetres, diastloic. The gait was characteristically "waddling" with the trunk hyperextended (Figure VIII). He was just able to rise from sitting on the floor by "climbing up the legs". The muscles of the lower limbs were large and were reminiscent of the muscles seen in pseudo-hypertrophic dystrophy. The muscles of the upper extremity in order of the degree of weakness were trapezius, rhomboids, biceps, triceps, brachioradialis, deltoid and *pectoralis major*. An electrocardiogram revealed only slight widening of the *QRS* complex.

Electromyography was carried out on June 30, 1952. The right brachioradialis and *extensor carpi radialis longus* muscles and the left *gluteus maximus* muscle were explored with a concentric needle electrode. No fibrillation potentials were seen at rest. During voluntary activity in the arm muscles examined, a very high proportion of the motor units recruited were pathologically short in duration, lasting one to three milliseconds. A histogram of action potential duration in seventy-four different motor units showed gross displacement to the left (Figure IX). During voluntary activity in the left *gluteus maximus*, no units lasting longer than 2·5 milliseconds were seen.

On July 16 examination of tissue from the left *vastus lateralis* revealed a histopathological picture of advanced dystrophy. There was a general loss of muscle striation. The muscle bundles showed patchy degeneration, some having undergone complete hyaline necrosis, and some were replaced by fat. In some areas there was localized proliferation of sarcolemmal nuclei. In scattered areas there were collections of chronic inflammatory cells (Figure X).

Treatment was begun on September 11 with mixed tocopherols, 300 milligrammes being given daily, and was continued for three months. At the end of this time he considered that the muscles were a little stronger, particularly those of the arms.

A further electromyogram on November 16 revealed a shift towards normal of the histogram of the action potentials from the muscles of the arm (Figure IX), but virtually no change in the tracings from the quadriceps.

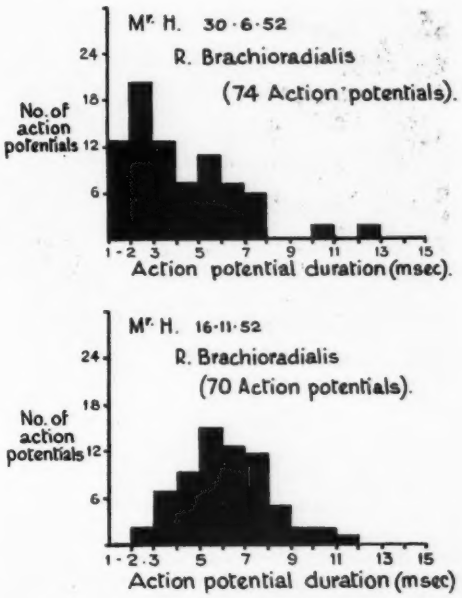

FIGURE IX

Case III. Demonstrating the shift to the right, towards normality, of the histogram after treatment with mixed tocopherols

Next two grammes of cortisone were administered orally as 25 milligramme tablets, one every six hours. After twenty days he admitted to no improvement in strength of the legs, but again considered that the arms were stronger. Another electromyogram revealed no further improvement. The administration of tocopherols was resumed for a further period of three months, but no change was noted. Because of the improvement in Case IV, a trial with testosterone was given. Clinically there was no improvement.

CASE IV.—M.D.G., a widow, aged fifty-one years, with one child had been under observation since 1948. At that time she suffered from cardiac infarction. In March, 1949, she was still suffering from cardiac pain

at rest and the blood pressure was 190 millimetres of mercury, systolic, and 130 millimetres, diastolic. Smithwick's operation was performed. This was followed by two years of relatively good health, during which she worked eight hours per day at a clerical occupation. In March, 1951, the blood pressure was 155 millimetres of mercury, systolic, and 90 millimetres, diastolic.

The present illness began in July, 1951, when there appeared a papular erythematous rash on her face and on the back of her hands. This rash persisted, but fluctuated in intensity for the following year. In August, 1951, she complained of aching in all limbs after exercise. In September, 1951, two apical abscesses were drained by extraction of two teeth. In October, 1951, she reported that the last menstrual period had been two days late and was scanty. There had been no further menstruation. The aching in

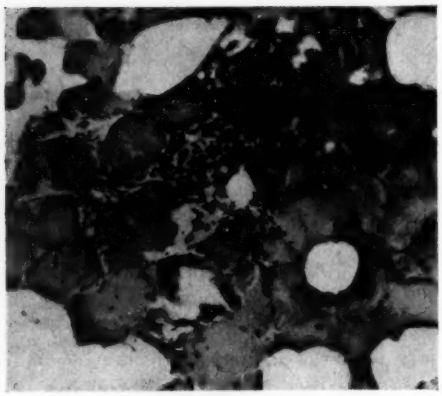

FIGURE X

Case III. Biopsy demonstrating selective degeneration and fat replacement of muscle fibres. Collections of chronic inflammatory cells are shown. (×100)

the limbs persisted, so that in September, 1951, she was forced to stop work as a typist because of pain in the arms. She suffered from loss of energy and malaise, and had lost 2·7 kilogrammes in weight. Persistent tachycardia (140 per minute) was present, but the rate slowed to normal during the first two days after her admission to hospital. By then there was obvious weakness in the muscles of the shoulders, arms, thighs and legs. Physiotherapy failed to help.

Muscular weakness progressed steadily, though the pain abated. By January, 1952, weakness was so great that she required help in getting out of bed, but once on her feet she was able to walk. During the greater part of the month she had intermittent difficulty in swallowing, with regurgitation of fluid through the nose. The rash on the face was at its worst and resembled the rash of *lupus erythematosus*. Symmetrical patches of erythemato-squamous dermatitis appeared on the elbows and on the posterior surface of the thighs. On January 29 a tumour was found in the right breast, together with an enlarged axillary gland. Biposy revealed an anaplastic infiltrating carcinoma of high malignancy, and radical amputation was carried out. Examination of sections of the axilla revealed infiltration of the areolar tissue outside the malignant gland. X-ray examination of the spine and pelvis revealed no evidence of metastasis. Amputation was followed by deep X-ray therapy. At operation the *pectoralis major* was noted to be pale and to contract poorly. Examination of a section revealed myopathic changes, but in view of the proximity to the malignant disease the significance of this was questioned.

In March, 1952, an electromyogram was taken in the left triceps. At rest no fibrillation potentials were seen. A thorough exploration of the muscle during voluntary activity revealed an almost total absence of normal motor unit potentials. There was an

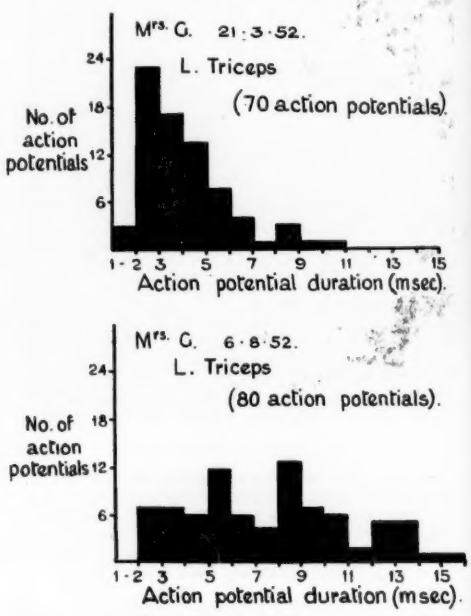

FIGURE XI

Case IV. Acute polymyositis. The shift to the right of the histogram following treatment with cortisone is demonstrated

abundance of highly polyphasic action potentials and action potentials lasting one to four milliseconds (Figure XI). The amplitude of these units was considerably less than normal.

Detailed muscle testing revealed great weakness of all muscles, except those below the knee and elbow. Minimal power (a flicker) remained in trapezius and rhomboids. Slightly stronger contraction was found in the *rectus abdominis*, the iliopsoas, the adductors of the thigh and the *gluteus medius*. The deep neck muscles, the sterno-mastoids, the supraspinati, the deltoids, the biceps, the brachialis, the remaining *pectoralis major*, the *glutei maximi*, the quadriceps and the hamstring groups were barely capable of their normal function of contraction against gravity.

Biopsy of the left quadriceps revealed patchy fragmentation and vacuolation of muscle fibres. In places there were small areas of necrosis. In other areas muscle cells were pale and swollen with loss of

transverse striation. Some muscle bundles were normal with well defined striation. There was a moderate increase in the number of lymphocytes round blood vessels (Figure XII). Another laboratory finding was a total serum protein content of 5·9 grammes *per centum* with a normal albumin-globulin ratio. The serum chloride, sodium and potassium contents were found to be normal (108, 135 and 5·0 milliequivalents per litre respectively).

Treatment was commenced on April 17, 1952, with mixed tocopherols, 300 milligrammes per day being given. After thirteen days there was no change in the electromyogram, though the patient considered that the strength was improving. After one month there was undoubted increase in muscle power. She was now able to pull herself up in bed to a sitting

FIGURE XII

Case IV. Biopsy of muscle demonstrating extensive degenerative changes. The pale area extending from the centre of the field to the right border is grossly degenerated and almost necrotic. Elsewhere striation has largely disappeared and there is increased cellularity. (×80)

position, a thing she had been unable to do for some few months. She could raise the extended leg off the bed seven times in succession—previously straight leg raising had been impossible. She was able to walk almost unaided.

The urinary excretion of creatine and creatinine in twenty-four hours was estimated on May 30 and on June 30, 1953. The amounts of creatine were 405 and 460 milligrammes per 100 millilitres respectively and those of creatinine 657 and 300 milligrammes per 100 millilitres respectively. (Normal figures are 0 to 200 and 400 to 1800 milligrammes per 100 millilitres respectively.) In June a search for *lupus erythematosus* cells were made, but they could not be detected by the methods of either Lee (1951) or Mathis (1951). By the end of June the rate of further improvement in muscle power was very slow. A muscle chart showed the weakest muscle to be capable of effecting joint movement against gravity.

Cortisone, 25 milligrammes every six hours, was administered orally for three weeks. After this treatment, there was no improvement on the muscle chart, though the patient considered some further power had returned. However, an electromyogram on August 6 revealed a considerable reversion towards normal (Figure XI).

An electrocardiogram and X-ray examination of the chest revealed no significant abnormalities. She was discharged from hospital on August 6 capable of independent activity. Treatment with mixed tocopherols, 300 milligrammes per day, was continued. By October the facial rash had almost disappeared. Persistence of a sinus in the right axilla and the development of pain extending down the arm led to exploration of the wound and biopsy in December. This revealed extensive inoperable malignant disease of the axilla, for which testosterone was administered parenterally in the dosage of 100 milligrammes three times a week.

Approximately three weeks after this therapy was begun, the patient noted considerable increase in muscular power, coincident with a feeling of well-being and loss of pain in the arm.

By the end of February, 1953, she considered that muscular strength had returned to normal. On February 27 an electromyogram revealed a virtually normal tracing. The administration of mixed tocopherols was stopped, but that of testosterone was continued. The malignant mass in the axilla became smaller and the wound healed. On April 28 a further muscle biopsy was performed. There was surprisingly little change in the histopathological picture, in view of the remarkable clinical improvement. The expected androgenic manifestations made their appearance.

By August the malignant disease was still well controlled. She had resumed all household duties and stated that she felt exceedingly well. In October she remained well, and a malignant cutaneous plaque over the lower end of the right sternomastoid had almost disappeared.

CASE V.—H.A.K., a farmer's wife, aged fifty-seven years, gave a history of progressive weakness in the legs over the preceding ten years. This was first noticed when she bent her knees a little whilst standing, and this was followed by her legs " crumpling up under her ", while at the same time she felt pain in the thighs. By June, 1952, when she was first examined, she was unable to climb stairs and was able to rise from a sitting position only with difficulty and by pushing on the arms of the chair. Her arms had gradually become weak also, so that she was quite unable to hang out the washing. She would rise from the floor by rolling on to her hands and knees and then pushing herself up with her arms.

Examination of the patient revealed no abnormality other than muscular weakness. The gait was characteristic. Electromyograms were made from the left *rectus femoris*, *vastus lateralis*, *tibialis anterior* and *extensor digitorum longus* muscles. At rest no fibrillation potentials were seen. Histograms of action potential duration of all muscles during voluntary activity showed a considerable displacement to the left, those of the thigh muscles being more displaced than those of the leg.

Muscle biopsy of the *vastus lateralis* on July 21 showed the muscle fibres to be indistinct in outline, some having a hyaline appearance. There was fragmentation of muscle fibre bundles in places, striation was poor and there was an increase of sarcolemmal nuclei in some fibres.

CASE VI.—D.B.F., a married woman, aged fifty-seven years, had been attending the out-patient department intermittently since the age of forty-five years. During these years she had complained of many symptoms which had been regarded, probably correctly, as neurotic in origin. The only abnormal finding had been a raised blood pressure, which had varied between 155 and 220 millimetres of mercury, systolic, and

95 and 130 millimetres, diastolic. When she was first examined by one of us on September 17, 1952, she gave the history of weakness in the legs present for approximately five years. Over the preceding six months she had felt too weak to do her housework and had suffered numerous falls. The last two months had largely been spent in bed. There were numerous other symptoms referable to almost every system, and many of these had been present throughout life.

The patient presented as a miserable elderly woman with the facies suggesting early myxœdema. The blood pressure was 150 millimetres of mercury, systolic, and 80 millimetres, diastolic, and albuminuria was present. There was very little weakness of the muscles of the shoulder girdle, but she was barely able to climb on to the examination couch. The gait was waddling. Trendelenburg's sign was present, and there was considerable weakness of the quadriceps.

Investigations revealed a negative response to the Wassermann test, a normal blood urea content, normal urea clearance, a basal metabolic rate of —8%, and a blood cholesterol content of 280 milligrammes *per centum*.

Electromyography showed great shortening of the majority of motor units from muscles in the arms and legs; but there were small patches which, with careful exploration, showed motor unit activity of normal duration.

Muscle biopsy of the right *vastus medialis* on October 15 showed some muscle fibres pale and shrunken; but the majority appeared normal with well preserved striations. This woman was considered to have early or mild muscular dystrophy, early myxœdema and neurosis. Treatment with thyroid was instituted, and was followed by considerable relief of most symptoms.

Electromyography was repeated on February 9, 1953. Changes indicative of a dystrophic process were still present, these changes being more pronounced in the muscles of the pelvic girdle.

Because of improvement and her return to household duties, thyroid medication has been continued since. Weakness in the legs persists, but is not sufficiently severe to incapacitate her or to warrant treatment.

ELECTROMYOGRAPHY

With a concentric needle electrode as used in this study, recording of activity is limited to a small volume of tissue within a few millimetres of the needle-tip. In this way it is possible to record activity in individual motor units or sub-units. Sherrington (1925) defined a motor unit as an individual motor nerve fibre together with the bunch of muscle fibres it innervates.

Obviously the anatomical arrangement of the motor unit within the muscle is of profound importance in studies of this kind. There is no certain evidence that all the fibres innervated by a single axon are grouped together in a single bundle, and attempts to elucidate this problem by simultaneous recording from different parts of the muscle have so far proved inconclusive (Kugelberg and Taverner, 1950). It is possible that activity in a fasciculus may represent the motor sub-unit as recorded by this method, since Wohlfart (1937) noted that in poliomyelitis muscle degeneration follows the pattern, not of muscle fibres, but rather of discrete muscle fasciculi, with fibres in adjacent fasciculi appearing undamaged. It is not clear, however, whether a single axon may innervate more than one fasciculus and whether such additional fasciculi may be widely distributed through the muscle.

The action potential so recorded is thus the summed action potential of the many muscle fibres forming the motor sub-unit. Whereas the action potential of a single muscle fibre has a duration of but one millisecond, the action potential duration of the sub-unit in most limb muscles averages five to eight milliseconds. However, since there is a very wide range of action potential durations in normal muscle, including both very long and very short, it is only by the statistical survey of a considerable number of different action potentials in a muscle that any conclusions can be drawn about the normality of the contractile tissue.

The initial surveys of action potential duration in normal and dystrophic muscle (Kugelberg, 1949; Petersen and Kugelberg, 1949) revealed a significant shift in the duration distribution curves towards the short side in many types of dystrophic musculature. However, Pinelli and Buchthal (1953) have found that the action potential duration changes in dystrophic muscle are rather more complicated than appeared from the initial studies of Kugelberg.

Buchthal and Pinelli (1953) point out that a decrease in mean action potential duration can by no means be regarded as specific for progressive muscular dystrophy. It was found in only two-thirds of their series of 32 cases. In the cases in which action potential duration was shortened there was no evidence of a familial incidence, and muscle biopsies showing an inflammatory reaction were confined to this group. In cases in which there was a normal or prolonged action potential duration frequently a familial incidence was present. Moreover, Buchthal and Pinelli report that shortened action potential duration occurs regularly in *dystrophia myotonica*, sporadically in disuse atrophy, and in *myasthenia gravis*, and that it was also seen in a case of generalized atrophy due to malnutrition. Indeed, a decrease in duration can occur without atrophy or dystrophy, as is exemplified by the findings in acute and chronic polymyositis (Buchthal and Pinelli, 1953).

On the other hand, there is evidence that in cases in which there is a shortened action

potential duration, as in thyrotoxic myopathy, the action potential duration tends to revert to normal with successful treatment of the causative condition (Sanderson and Adey, 1952). In two of the cases in the present study there has occurred a reversion of the duration curve towards normal, with a concomitant clinical improvement, although the biopsy appearances after therapy were not significantly improved.

The shortening of action potential duration has been ascribed to a variety of causes. It was originally suggested that in dystrophic muscle it might result from a reduction in the number of muscle fibres innervated from a single axon (Kugelberg, 1949). Certainly in advanced dystrophy the action potential duration is only about one millisecond, or about the same as that for a single fibre. More recently Pinelli and Buchthal (1953) have denied the role of reduced temporal dispersion as a factor in the reduction, and also discount such factors as atrophy, inflammation and shortening in the functional length of the fibre. They suggest that it may result from a general increase in propagation velocity of the impulse over the muscle fibre, and that this may be the consequence of an existing or previous inflammatory reaction.

DISCUSSION

The object of this paper is to draw attention to cases of muscular disease that have largely been overlooked in the past. But for the paper of Shy and McEachern (1951), the cases reported above would have continued to pass unrecognized.

The ætiology of the disease is obscure. In none of these cases was there any family history of muscular disorder, or any information to suggest the adult form of the well recognized juvenile muscular dystrophy. The pathological changes found in the muscles are patches of necrosis, degeneration of individual fibres or groups of fibres and finally fat replacement. Shy and McEachern regard these changes as those of a muscular dystrophy, whereas Adams, Denny-Brown and Pearson (1953) consider that they are the changes of non-specific patchy inflammation, a condition of chronic polymyositis. The clinical pictures described by these two groups of authors differ somewhat. In the present series, the diagnosis in Case IV was probably acute polymyositis. Initially there was pain with tenderness of muscles, tachycardia and a transient pyrexia, signs suggesting an inflammatory disorder. This case was complicated by hypertension, previously controlled by sympathectomy, and subsequently by the development of a carcinoma of the breast, but without more than local metastasis. Either of these conditions may have had an ætiological relationship to the disease of muscle. The illness was also accompanied by a rash resembling that of *lupus erythematosus*. This suggests that it may well have been a collagenous disease, though there was no histological or laboratory evidence that would place it in any of the recognized groups such as disseminated lupus or polyarteritis. The course was one of gradual recovery, and it is impossible to assess the therapeutic value of cortisone, tocopherols or testosterone. Muscle strength returned almost to normal and the electromyogram eventually became normal, though paradoxically the biopsy revealed no improvement. This case presents a clinical picture similar to that described by Adams *et alii* (1953) as polymyositis.

The remaining five cases, however, presented an entirely different clinical picture. The onset was in all extremely gradual, and there was no history in any of pain or tenderness in muscles, such as one might expect with an inflammatory lesion, of which we were seeing the end results. The clinical picture of all followed the pattern described by Shy and McEachern under the term "menopausal muscular dystrophy", and that pattern is one of a degenerative or dystrophic process, rather than of an inflammatory one.

Electromyographic studies fail to differentiate the two disorders, if indeed they are different entities. Both groups show significant shortening of motor unit potentials.

Definite differentiation should be possible from study of biopsy material, but in this respect opinions differ. The picture differs from that of the juvenile form of dystrophy, in which there is a progressive atrophy with great variation in size of muscle fibres, except in the pseudohypertrophic form in which there is gross fatty replacement as well. Shy and McEachern regard the changes found as characteristic of a particular form of dystrophy, whereas Adams *et alii* consider they are due to polymyositis. The similarity of the findings in our case of polymyositis with those of the other five are in favour of the latter being primarily inflammatory. Figure XII, a section from a muscle in the case with acute onset (Case IV), shows similar pathological changes to those seen in Figures III and IV, sections of a specimen taken from a patient who had had the condition for five years. In Figure X is shown a collection of small round cells, found in muscle which had been weak for thirteen

years. Such findings would appear to indicate persistence of an active disease process. Thus the differentiation of "polymyositis" from "menopausal muscular dystrophy" would appear to be a clinical one only. If cases of the latter are in fact due to polymyositis of extremely insidious onset and slow progress over years, then the two disorders become merely varieties of the one disease.

Christensen and Levison (1950) reported six cases of polymyositis. In one, in which serial muscle biopsies were made over three years, they noted that inflammatory changes disappeared "leaving features of peripheral muscular dystrophy". Such cases support the contention that "menopausal muscular dystrophy" may be the late result of chronic polymyositis and therefore not a true dystrophy, which is commonly accepted as a primary degeneration of muscles.

In the present series creatine excretion was estimated in three cases. In one only, the acute case, was there a higher value than normal. The findings in the other two are comparable to those of Shy and McEachern and are lower than one would expect in muscular dystrophy. The latter authors draw attention to the similarity of the pathological changes in "menopausal muscular dystrophy" with those found in the muscles of animals rendered dystrophic by vitamin *E* deficient diets.

The results of treatment have been difficult to assess and in general disappointing. Tocopherols have been used as a therapeutic measure in muscular disorders since Olcott (1938) demonstrated the histopathological changes of dystrophy in the muscles of vitamin *E* deficient rats. Results of their use in human material have been variable. Rabinovitch, Gibson and McEachern (1951) reported remarkable improvement in three of five cases of "menopausal muscular dystrophy". In the present series 300 milligrammes of mixed tocopherols were given daily to four patients. In Case II there was no improvement. In Case IV, the acute case, there was clinical but no electromyographic evidence of improvement. In Case III, the patient, a male, reported increased strength in the arms, and this was supported by a shift towards normal of the histogram of action potential durations obtained from the brachioradialis (Figure IX). There was no improvement in the muscle of the pelvic girdle.

Case I is more convincing; but administration of tocopherols coincided with convalescence from a pulmonary embolism, and at least some of the improvement may have resulted from the resumption of activity after rest in bed for several weeks, and the natural improvement of muscle function. However, the shift towards normal of the histogram obtained from the *vastus medialis* (Figures II and V) and the overall improvement leave little doubt but that tocopherols were beneficial.

Cortisone was given in three cases, its value having been reported by Shy and McEachern (1951). In Cases II and III there was no evidence of improvement clinically or electromyographically. In Case IV improvement was noted and confirmed by electromyography (Figure XI). This was the acute case, and some clinical improvement had already begun, concurrently with the use of tocopherols. It is impossible to state whether further improvement resulted from, or was merely coincidental with, the use of cortisone and later of testosterone. An interesting feature of this case was the obvious dissociation between muscle function and structure. Muscle strength and the electromyogram became virtually normal; yet biopsy revealed no diminution in the extensive degenerative changes. This raises the question as to the degree to which recovery of the affected muscles may be possible. In two cases (I and II) in which improvement after administration of tocopherols was demonstrated, the muscles least affected electromyographically showed the greatest improvement. Thus in Case I recovery in the quadriceps muscles, which were least affected at the initial examination, was virtually complete (Figure V), whereas in the glutei there was very little improvement. Likewise in Case III recovery of function in the brachioradialis was moderate (Figure IX), whereas there was no improvement clinically or by electromyography in the quadriceps, the muscles most severely involved.

Another finding of interest is the selective affection of various muscles. In general the proximal limb muscles and those of the pelvic and shoulder girdles bore the brunt of the disease. Even amongst these groups of muscles there is evidence of selective involvement. This is best demonstrated in Case II, in which the *vastus medialis* was virtually normal by all tests including biopsy, yet the surrounding muscles showed gross changes clinically and microscopically. In this respect there is a resemblance to the selective involvement of muscles seen in the juvenile muscular dystrophies. It would appear that herein is to be found a key to the disease process. With more adequate biochemical and histochemical techniques the minute differences characterizing the intimate metabolism of individual muscles may be elucidated, or at least some basis found for the selective distribution of the disease.

SUMMARY

Six cases of myopathy occurring in people of middle age have been described. Five of these conform to the disease described by Shy and McEachern (1951) as menopausal muscular dystrophy. There were muscular weakness without wasting, confined to the proximal muscles, electromyographically demonstrated shortening of motor unit action potentials and histopathologically patchy degeneration of muscle.

The sixth case was one of acute polymyositis with similar electromyographic changes and patchy necrosis of muscle, but with an acute clinical picture.

The significance of the electromyographic findings has been discussed. They are consistent with the diagnosis of either muscular dystrophy or chronic polymyositis. The histopathological picture of biopsy specimens is that of menopausal muscular dystrophy, but may well be the end result of non-specific inflammatory lesions.

Clinical and electromyographically demonstrated improvement followed the use of mixed tocopherols in two of four cases.

Cortisone was administered to three patients. Only one improved with this treatment and it is impossible to assess the value of cortisone in this case.

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THYROTOXIC PERIODIC PARALYSIS[1]

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DIFFICULTIES in diagnosis may arise when the only symptom of which a patient complains has not been previously described, or when such a symptom dramatically overshadows the usual manifestations of disease.

An unusual presenting symptom, specific and easily recognizable, has prompted the description of the following cases.

CASE REPORTS

CASE I.—A man, aged twenty-nine years, made the following statement:

> Two months ago I was visiting friends. On attempting to rise from a deep-seated lounge chair in which I had been sitting before a fire for a couple of hours, I felt a stiffness in the lower part of the back, accompanied by an almost negligible twinge of pain—something like a touch of lumbago, I should imagine. This occurred two or three times during the following week, and the feeling of stiffness extended to my thigh muscles at times. This sensation was apparent on rising to my feet from a sitting position, and only after I had been seated in a deep-seated lounge chair before an open fire.
>
> The first severe attack occurred one night at the end of a picture show. The seat was of a lounge chair type with deep cushions. I made as though to rise to my feet, but nothing happened. I was completely powerless from the hips down. I tried again, this time straining my leg muscles to their utmost, but I was quite unable to rise. Then, pushing with my arms on the arm rests, I forced myself into an almost standing position, supporting my weight on my arms. My legs were quite unable to support my weight no matter how hard I tried to stand. In effect they just dangled uselessly. Then I found that by forcing my knees back and stiffening my legs I could stand in this position, and I endeavoured to walk with knees braced. I had a feeling that, once my knees bent, my legs would not support me and this was so, for having scarce taken two steps, one knee bent and I plummetted to the ground as though my legs had been jerked from beneath me. On the floor I found great difficulty in moving at all—with my arms I was able to raise my upper body, but from the hips down I was powerless. I was able to sit on my buttocks but could not rise to my feet. I crawled slowly along the floor with an uncertain dragging motion of the knees, but it was exhausting work and I could not have gone far. With my wife's assistance and the aid of the theatre seats (the theatre by this time was quite empty) I regained my feet, and keeping my knees braced was able to hobble from the theatre after a few falls. My wife and a taxi-driver managed to get me into a car and on arriving home it was necessary to carry me indoors and lay me on my bed. I was unable to undress myself owing to inability to raise my legs.
>
> During this attack I had no sensation whatsoever of any pain nor did I notice any abnormality whilst sitting down prior to rising, other than a feeling of heaviness in my legs when shifting my position, which I later came to recognize as an indication that an attack was on. My legs were quite sensitive to pain when I pinched my thigh. As after all subsequent attacks, I was completely normal after a night's sleep.
>
> The second attack occurred at home a few evenings later—again after having been seated for some time in an arm-chair before the fire. Again I could not rise, and, after levering myself to my feet with knees braced, took two steps and slumped to the floor. Once down I could not rise unaided.

The remainder of the history may be paraphrased. The symptoms recurred on subsequent evenings, commencing whenever he sat long enough. As time went on the condition occurred earlier in the day, and on his sitting for shorter periods. Some six weeks after the onset he found difficulty in rising from the table after his evening meal. After a severe attack on the previous night his knees would seem weak in the morning, but would gradually strengthen during the day. After another three weeks the difficulty in rising occurred at work whenever he sat for longer than an hour. His journey to and from work involved an hour's travel by train. Two evenings before examination he had to be helped from the train, and fell on the platform. The next morning on his way to work he was unable to rise from the seat at the correct station, and was carried on by the train. During attacks on the last few evenings he noticed difficulty in grasping objects, and once when trying to pull himself up from the floor he found that his arms were weak. It may once again be stressed that attacks occurred only on his attempting to rise from a sitting position. While sitting he noticed a preliminary slight weakness in the thigh muscles when he shifted his position, and he was able to move his legs but they were noticeably heavy. He could not lift his feet from the ground. He had lost nine kilogrammes in weight, and he had a persistent feeling of nervousness and agitation. His hands trembled visibly. Previously sensitive to cold, he was now comfortable with less bed clothes at night and lighter clothes during the day. His face began to look drawn. Shadows appeared under his eyes, which developed a more than usually protuberant appearance, although this had always been a facial characteristic.

On examination of the patient, slight exophthalmos was present, and the eyes were staring, with wide palpebral fissures. There was lagging of the upper lids during downward movement of the eyes. The thyroid gland was soft and slightly enlarged. The pulse rate was 132 per minute; the blood pressure was 120 millimetres of mercury, systolic, and 90

[1] Received on May 3, 1954.

millimetres, diastolic. There was tremor of the outstretched hands. The deep reflexes in the upper limbs were poor, and those in the lower limbs brisk.

Admission to hospital was arranged without delay. Unfortunately no attacks occurred while he was in hospital, nor was it possible to produce attacks by prolonged sitting in a suitable chair during the evenings, or by prolonged venous compression (by a sphygmomanometer band) or temporary arterial compression.

The basal metabolic rate was +79%, the increase being confirmed at a second reading. Electromyography revealed no abnormality either before or after operation. Subtotal thyroidectomy was performed by Mr. G. R. A. Syme, under "Avertin" anæsthesia. The thyroid gland was vascular, friable, and larger than was expected from palpation before operation. Microscopic examination of the gland showed the alveoli to be variable in size and shape. The epithelium was composed of cells, ranging from cuboidal to columnar in shape, with papillary formation. Specimens of muscle removed from the neck and the right *vastus lateralis* were normal on microscopic examination.

Four days after operation the tremor and headache had disappeared, and subsequently he remained free from symptoms. The basal metabolic rate two weeks after operation was +3%.

CASE II.—A male patient, aged thirty-nine years, was referred for examination because he used to collapse at times, though he never lost consciousness. Three months previously he had noticed weakness of his legs on arising from his seat at a cinema. When he attempted to go down stairs from the dress circle his legs suddenly gave way underneath him, as if his knees had been suddenly struck from behind. While he was struggling to get up, a bystander helped him to his feet. Once he was upright he was able to remain so, and was able to descend the stairs by holding on to the rail. However, when stepping off the kerb he again fell. Thereafter he walked home with his wife's assistance, keeping his knees straight. The condition disappeared during sleep.

Two weeks later he felt the same weakness when rising from his seat in a tram. He fell while alighitng, hitting his head on the road and breaking his glasses. As soon as he was helped to his feet he was all right. He fell on six subsequent occasions, always after sitting. The longer he sat the greater the subsequent weakness. If he sat for more than ten minutes he had to push himself up with the aid of his arms; if he sat for more than twenty minutes he was likely to fall. He therefore took care to get up each ten minutes or so. Later he found that straightening his knees from time to time while sitting made it possible to sit for longer without collapsing on arising. There was no sensory abnormality. In between the attacks he played squash racquets actively.

In response to direct questioning, the patient said that his eyes had protruded during the last fifteen years, and the degree of protrusion had not increased recently. A swelling had been present in the neck for the same length of time. He perspired a good deal. He had no preference for hot or cold weather. He commenced to lose his hair when aged nineteen years. (His father was completely bald.) There was no alteration in libido, nor was there a family history of cataract, and he had five healthy children. His sister had had two operations for goitre.

Pronounced bilateral exophthalmos with lid retraction was present. There was no swelling of the lids, œdema of the conjunctiva, or weakness of ocular movements. The thyroid gland was diffusely enlarged. Slight digital tremor was present. The pulse rate was 100 per minute, and the blood pressure was 140 millimetres of mercury, systolic, and 90 millimetres, diastolic. There were no abnormal neurological signs, nor could any evidence of muscular weakness be found. The basal metabolic rate was +56%. Thyroidectomy was performed by Mr. T. Ackland. The gland was found to be diffusely enlarged, and the histological findings were typical of exophthalmic goitre. He has been well since operation, his eyes have not been staring, and he has had no subsequent attacks of weakness.

This symptom has been noted along with other evidence of muscular involvement in several cases of thyrotoxicosis. The patient did not refer to the symptom until questioned—nor is it present in every case. In one patient it served as a warning that the disease was not progressive muscular atrophy and directed attention to evidence of thyrotoxicosis which would otherwise have remained unnoticed. Thus the symptom was of assistance in a type of case which, while rare, is subject to misdiagnosis. Since the outlook in the two conditions could hardly be more different, correct diagnosis is of the greatest importance.

Two further examples are associated with more protean symptomatology and with thyroid disorder of less definite type.

CASE III.—In November, 1946, a medical practitioner, aged forty-five years, noticed a sudden catch when straightening his knees after sitting. It seemed to him to be due to cramping of the *quadriceps femoris* when the knee was semiflexed, disappearing when he was erect. On January 5, 1947, he was somersaulting on the beach and landed on the back of his neck. On the next night, when visiting, he was rising from a chair when his knees seemed to cramp and he fell back into his chair. After he had risen from the chair a moment later, with the assistance of his arms, the cramp recurred. When he lifted his knee to go up a step he fell down. However, he was able to reach his motor-car and drive home. When in bed, at 11 p.m., he found that he was losing the power of all his limbs. The onset was so abrupt that the diagnosis of poliomyelitis came to the patient's mind. Paresis increased over the next two hours, until he was unable to move. At 9.20 the next morning he was reclining, exhausted by his efforts to rise, when he suddenly thought of something which he wanted, and found himself sitting up. He was then able to move all muscles, and felt all right, except for some stiffness.

He next went away for a holiday, when he thoroughly enjoyed severe exercise each morning. Towards evening, however, he felt increasing stiffness until it was agony to go up steps. When seated, he found it necessary to lift his thigh with both hands in order to cross his legs. This was always worst towards evening. Some three weeks later he was trying to rise from a chair with the aid of his arms, when he found that his arms would not take his weight, his thighs cramping at the same time. He also noticed that the grip of his right hand was weak. When in bed at 2 a.m. he again found that he could not move. At 8 a.m. the paresis disappeared, except for slight stiffness. He also noticed difficulty in differentiating between hot and cold water over his legs. A week later another

slight attack occurred at 6 p.m. and passed off at 6.30 a.m. He now felt very weak when walking and ran " like an old woman ". On stairs his knees " felt like a drunk's knees ". He also noticed difficulty in swallowing dry bread. He often " had to bring it forward ", and swallow again.

He stated that his eyes had " always " been somewhat prominent. The only other abnormality found on examination was tenderness of the *quadriceps femoris* on compression. The blood potassium level estimated during an attack was normal, and potassium chloride given by mouth (one teaspoonful three times a day) failed to modify the condition in any way. The urinary creatinine excretion was normal.

He was admitted to the Repatriation General Hospital, Heidelberg, and I am indebted to the Repatriation Commissioners and to Dr. John Bolton for details of his subsequent course.

Some four months after the onset he complained of seeing double and the left eye was noticed to become more prominent. Ptosis of the right upper eyelid, bilateral lid retraction, chemosis and diplopia on lateral deviation were present. The basal metabolic rate on three occasions was +12%, +15% and +20%, and digital tremor was present. The thyroid gland increased slightly in size. Dr. Bolton considered that he suffered from exophthalmic ophthalmoplegia rather than from thyrotoxicosis.

" Prostigmin " given by injection and by mouth had no effect upon the muscular weakness or on the proneness to attacks. Thyroid extract, taken by mouth, increased the weakness. Stilbœstrol, however, appeared to reduce the frequency and intensity of the symptoms and the proptosis diminished.

The symptoms continued and his own description may be appended.

> When this feeling of weakness came on I felt I had to automatically raise one thigh after the other in order to counter this. I particularly noticed it whilst at the pictures and at interval, when I tried to rise, I had a cramp-like pain in the *quadriceps femoris*. This pain disappeared on standing stiff-legged, but reappeared when I bent my legs to walk downstairs to the foyer. I found that if, at intervals, I walked stiff-legged for a few hundred yards the weakness sometimes left me altogether. On returning to the theatre I felt well, but the condition might recur during the second picture. Any nervous excitement such as a thrilling picture, or even cold weather, would tend to make the attacks worse. I noted that my worst attacks of paresis occurred after visiting pictures even though I felt quite well prior to going to the theatre.
>
> While touring late in 1947 I felt well until I went to the pictures at Lakes Entrance. After the show my wife and daughter had to practically carry me home because my legs would not move. I had a severe attack of paresis all night, in which any effort to turn over would only be made at great expenditure of energy and the pulse rate rising to 130 and more. In the morning, about 8.30, I attempted to stand stiff-legged at the side of the bed and this brought on a distinct feeling of nausea and faintness, which passed off rapidly on lying down, after passage of flatus. About 9.30 a.m. I could feel the paresis wearing off, and I was able to stand stiff-legged and shave, and later dress with difficulty. At 10.30 a.m. I was able to drive my car, lifting my thighs with my hands in order to get my feet on to the pedals. After driving 20 miles I walked around naturally, with no ill effect apart from a feeling of utter exhaustion. I then had no trouble for another week. As a rule the bouts of paresis appeared periodically, occurring about once weekly, though I had many bouts of quadriceps cramps and minor attacks of weakened thigh muscles in between.

He continued to take stilbœstrol, although it produced depression and uncomfortable hypertrophy of the breasts. (He takes 10 milligrammes three times daily for three days, and gradually reduces the dosage over a period of three weeks, together with one cubic centimetre of " Calcium Ostelin " by injection. Such courses are repeated each three months.)

The last severe attack of muscular weakness occurred in September, 1951; but he still suffers from muscular weakness after sitting in a theatre seat. The tendency, he believes, increases a little towards the end of the period of freedom from medication with stilbœstrol. The proptosis remains as it was before the onset, and there is diplopia on looking upwards.

In August, 1953, the thyroid panel of the Royal Melbourne Hospital found the uptake of I^{131} and the PBI^{131} were normal, while the protein-bound iodine estimations were also within normal limits. Thus there was no evidence of thyrotoxicosis at this time, or during a second series of observations.

CASE IV.—A man, aged thirty-three years, stated that eighteen months before he had noticed slight difficulty in fielding during a cricket match. He could only describe it as an unusual stiffness " as if he had suddenly grown older than he should have been ". It made him decide that he should have a holiday. On the first night of the holiday, after sitting in a chair, he hobbled into bed feeling " as stiff as a board ". During the night he awakened on several occasions, and when he attempted to turn over his legs would not turn with his body and he had to move them with his hands. In the morning his legs would not move, but the weakness gradually decreased and disappeared by 2 p.m. A second attack occurred two weeks later. On this occasion, after sitting intermittently in an armchair for three hours, he arose with difficulty and had to walk in a stiff-legged fashion. When he stepped down from a verandah his knees gave way underneath him and he collapsed heavily. Again he spent an uncomfortable night, and only by 11.30 a.m. was he able to struggle out to his motor-car to drive to see his doctor. Subsequently he found that sitting for half an hour in a chair at the end of the day would induce an attack. This would lead him to expect difficulty during the night, but sometimes this difficulty did not materialize. While at the pictures he found that he could postpone the attack by moving his legs and wriggling his body. In the worst attacks his arms became affected.

He had lost five kilogrammes in weight in six months. He had always disliked hot weather. His thirst had increased in the last six months, and his wife told him that he was eating more salt than usual.

Examination revealed a mild degree of bilateral proptosis with mild lagging of the upper eyelids on downward movement of the eyes. The lateral lobes of the thyroid gland were slightly and diffusely enlarged.

As the attacks had ceased in two previous cases on the patients' admission to hospital, so preventing further theoretically important investigations, it was decided to postpone this patient's admission to hospital as long as seemed reasonable. On the evening of his being examined he was taken to the pictures, and

arrangements were made for taking blood for observations of serum potassium and sodium, and for giving "Prostigmin" by injection. However, although attacks had occurred the previous day, no attack occurred, nor on the next day did sitting in an armchair for prolonged periods produce attacks. Estimation of the PBI^{131} content of the blood plasma forty-eight hours after administration of the radio-isotope resulted in a figure of 0·73% of the dose per litre of plasma, suggesting hyperthyroidism. He lived in a remote part of Tasmania, and arrangements were made for the taking of appropriate specimens during attacks.

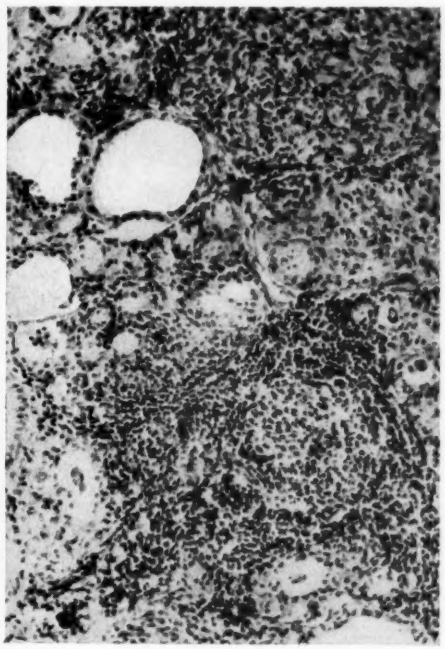

FIGURE I

Small vesicles and groups of pale thyroid cells are almost lost in the accumulation of lymphocytes, one lymphoid follicle being present. Several acini contain single cells or groups of cells in the lumen. (×130)

However, even though his admission to hospital was delayed for four months (part of this being to suit the patient's convenience), only one attack occurred, and unfortunately the specimens of blood taken during this attack were unsatisfactory for examination. The patient believed that taking potassium lessened the severity of this attack, but this could not be asserted with certainty. Finally he was admitted to hospital, and in spite of a further month's delay in operation no attacks occurred. The patient occasionally had a temperature of 101° to 102° F., lasting for twenty-four hours, during the last two months of this period, and sometimes he had three or four bowel actions per day. While in hospital his temperature only twice rose to 99° F., and his sleeping pulse rate was between 72 and 84 per minute. The basal metabolic rate was +4%, +31% and +39% on three occasions. The uptake of I^{131} was found to be in the toxic range of values, as was the protein-bound iodine estimation. The level of PBI^{131} in the plasma was not significant of abnormality. The thyroid panel of the Royal Melbourne Hospital considered these results to be "somewhat in favour of thyrotoxicosis". The blood cells were normal except for lymphocytosis (small lymphocytes, 46·5%). The serum potassium content was 18 milligrammes per 100 millilitres (4·6 milliequivalents per litre), and the serum sodium content was 310 milligrammes per 100 millilitres (135 milliequivalents per litre).

On September 8, 1953, Mr. G. R. A. Syme removed the greater part of a slightly enlarged, tough, fibrous thyroid gland.

Dr. J. D. Hicks, Pathologist to the Royal Melbourne Hospital, provided the following report upon, and evaluation of, the pathological appearances:

Thyroid gland: The substance of the thyroid gland was of even texture and the vesicles were of about normal size, but there were several areas slightly paler in colour than the major portion of the gland.

Histological examination: More than two-thirds of the gland consists of vesicles which are within the normal limits of size and height of epithelium. Some lobules, often near the periphery of the gland, are composed of smaller vesicles lined by lightly-stained columnar cells. Generally, these areas are infiltrated by lymphoid tissue, sometimes as follicles with pale reactive centres, but also as lymphocytes spreading loosely around and between the small vesicles and groups of pale thyroid cells (Figure I). Individual mononuclear cells or a small compact group of cells are seen within the lumen of a few vesicles near the edges of these cellular masses.

Comment: The pathological changes do not suggest a simple hyperplasia; rather the appearance is that of a mild chronic thyroiditis. There is no fibrosis such as is found in Riedel's struma, and the degree of lymphoid hyperplasia is not so gross as to suggest Hashimoto's disease. The vesicles are not disrupted by the more active subacute inflammation of the giant cell thyroiditis described by De Quervain.

Muscle: Groups of fibres from the sternohyoid muscle are of normal appearance, but between the muscle fibres in the specimen obtained from the *quadriceps femoris* there are numerous cellular infiltrations (Figure II). The majority of the cells are small darkly-staining lymphocytes, generally in groups of half-a-dozen about a small vessel and as single cells surrounding muscle fibres. In parts there is also accumulation of larger pale ovoid cells which extend along vessels and between muscle fibres. Most of the muscle fibres are quite normal but there are a few striking changes. A necrotic fibre surrounded and infiltrated by leucocytes is shown in Figure III. The cells are mainly mononuclear but lymphocytes and a few polymorphonuclear cells are present. Fragments of the disintegrating fibre remain amongst the leucocytes. In some affected fibres there is enlargement of the nuclei of the muscle which become more central in situation. Some typical multinucleated muscle giant cells are seen. It is difficult to determine what changes have taken place in the muscle fibres in relation to the larger leucocytic infiltrations. Some fibres appear to be atrophic or partly replaced by fibrous tissue, but there is often little change.

Comment: The acute necrosis of the muscle fibres and the lymphorrhages are by no means specific, for both necroses and lymphorrhages are present in a number of conditions such as severe toxæmias. They may be present in rheumatoid arthritis and, of particular interest in this case, have been described in *myasthenia gravis* (Russell, 1953).

Whether chronic thyroiditis produced over-secretion of toxic substances, or whether the lymphocytic infiltration merely occurred during the course of exophthalmic goitre can hardly be stated.

FIGURE II

Many groups of lymphocytes and mononuclear cells lie between the muscle fibres of the *quadriceps femoris*. (×78)

In a remarkable early paper Dudgeon and Urquhart (1926) described lymphorrhages in the muscles of eight out of nine subjects of exophthalmic goitre. These varied from a few cells aggregated together between muscle fibres to a wide tract of mononucleated cells extending for a considerable distance and producing wide separation of the fibres. The cells were large and small lymphocytes, with a few endothelial cells and plasma cells. The interstitial cells often proliferated, and not infrequently chronic interstitial myositis with atrophy of muscle fibres was a pronounced feature. The changes were most marked in the ocular musculature. The thyroid gland had the usual appearances of exophthalmic goitre, and in four out of nine cases lymphoid tissue in the thyroid was a marked feature. Muscular symptoms were mentioned in only one case, the exophthalmic goitre being, they state, associated with *myasthenia gravis*. The authors draw attention to the similarity of the muscular findings to those of *myasthenia gravis*.

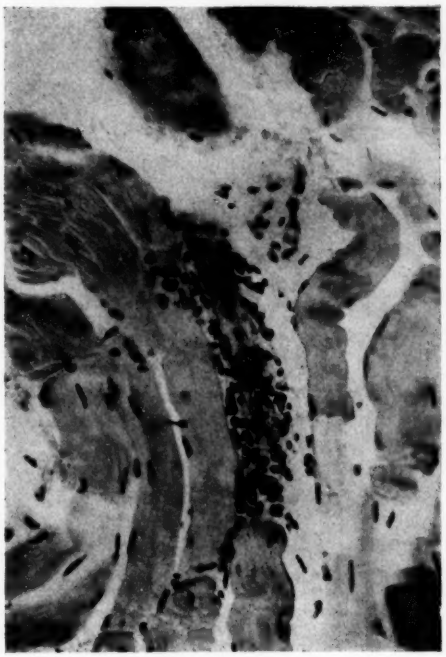

FIGURE III

Degenerate muscle fibre infiltrated by leucocytes which include a few polymorphonuclear cells. Two nuclei are large and lie within the remaining sarcoplasm. (×270)

DISCUSSION

W. Russell Brain (1938) classified the muscular disorders associated with hyperthyroidism in the following manner:

I. The thyrotoxic myopathies.

(*a*) Acute thyrotoxic myopathy ("acute bulbar palsy complicating exophthalmic goitre").

(*b*) Chronic thyrotoxic myopathy ("progressive muscular atrophy complicating exophthalmic goitre").

(c) Thyrotoxic periodic paralysis ("periodic paralysis complicating exophthalmic goitre").

II. *Myasthenia gravis* associated with exophthalmic goitre, the muscular disease being identical with that which occurs without hyperthyroidism.

The inability of a previously strong person to rise from a chair after prolonged sitting is a striking symptom. It was the only muscular symptom in two cases, and in two others it merged into increasing paralysis during the night. The symptom was not produced by muscular usage, as in myasthenia, nor was there permanent muscular weakness, as in thyrotoxic myopathies. The symptom described is a periodic paralysis, its brevity and isolation making it remarkable. This condition is not familial, and the question arose as to whether the symptom was typical of family periodic paralysis.

A small number of cases of periodic paralysis with hyperthyroidism have been reported. The symptoms have been stated by all authors to be typical of family periodic paralysis. Morrison and Levy (1932), for example, described a patient as being "awakened at night by a peculiar paræsthetic phenomenon over the lower extremities. On attempting to rise, he found he could not move. The condition lasted for three hours and then cleared up as rapidly as it had commenced. Following the attack, the patient felt tremulous and weak, and for a short period was markedly unstable on his feet, but he suffered no physical pain". In the attacks the skeletal musculature was hypotonic throughout, there being a flaccid paralysis of all four extremities. Exophthalmos and thyrotoxicosis were present, the basal metabolic rate being +50%. The attacks continued with diminishing frequency and intensity after thyroidectomy.

Dunlap and Kepler (1931) suggested two possible explanations of this condition: (i) that there is a latent tendency to develop familial periodic paralysis, exophthalmic goitre acting as a precipitating factor; (ii) "there may be some physiologic or chemical change occurring in the muscles in cases of exophthalmic goitre, which is not understood, and which is directly responsible for the production of transient paralysis in these cases".

Taylor (1898), in an outstanding early paper on family periodic paralysis, mentioned the frequency of onset during sleep. He stated that muscular exertion, followed by muscular rest, is the condition for an attack. Talbott (1941), while reviewing all recorded cases of periodic paralysis, including thyrotoxic cases, did not mention weakness after sitting in a chair. He described the patient's awakening paralysed, and adds that "more rarely, attacks begin during the day in the pursuit of routine duties". Nor in other recorded cases is the inducing effect of sitting mentioned. It seemed possible, however, that this symptom claimed attention because it was an isolated presenting symptom. Search of the writer's own histories of subjects of family periodic paralysis showed that the symptom was mentioned in seven of 11 cases. However, it remained outweighed in significance by the sleep paralysis. One patient stated that if she danced two dances and then sat down, she would be unable to move and would be paralysed for a day. If she kept on dancing she stiffened up more gradually. On other occasions her knees would give way when she attempted to rise from a chair in the evenings, and if she was alone, she would have to crawl to bed on all fours. The paralysis might, or might not, increase during the night. Another patient stated that the attacks commenced with difficulty in arising from a chair after sitting by a fire in the evening, and after sitting at the cinema. Finding it an effort to arise from a chair in the evening allowed another patient to forecast nocturnal attacks of paralysis. Another found his legs powerless on rising from a cinema seat on a cold night, and had to go home by taxi.

Hence, the symptomatology of familial and thyrotoxic cases is similar. Taylor, in 1898, perceptively wrote that the word disease should be used with caution as applied to family periodic paralysis.

> The tendency to dignify a symptom or a group of symptoms by calling it a disease entity has already been productive of much confusion of nomenclature in relation to affections of the nervous system whose pathology is obscure. As stated at the outset, the term "family periodic paralysis" is purely clinical and descriptive, and should be definitely so understood. If through a certain poverty of words we occasionally speak of the symptom-complex under consideration as a disease, it is merely as a matter of convenience, and in no way as indicative of a dogmatic belief that a periodic paralysis, as such, can in itself represent a pathological entity. Our feeling, rather, is that we are dealing here merely with a symptom, or symptoms, of extraordinary constancy, whose etiology and pathological anatomy are as yet wholly obscure.

Talbott's conclusions are similar. He states that the symptom complex is characterized by periodic paralysis, loss of reflexes and loss of electrical excitability. It "appears as an hereditary trait in certain families, sporadically in susceptible persons, in association with

thyroid disease or malaria, and following a high carbohydrate meal during excessive assimilation of desoxycorticosterone acetate in the treatment of Addison's disease ".

Evidence exists that family periodic paralysis is intimately linked with potassium metabolism ; but metabolic study of patients with thyrotoxicosis are wanting, and unfortunately could not be made in the cases here reported. It is possible that the muscular symptomatology accompanies abnormal potassium metabolism, which may be produced by different conditions. It is of interest that the microscopic appearance of the muscle in Case IV is different from that described by Goldflam (1895) in family periodic paralysis ; but this point is not of crucial significance, for the duration of the disease was different, and thyroid disease may add its own pattern—the cellular abnormality being related to, rather than being a direct cause or product of, the metabolic disorder. Chronic thyrotoxic myopathies again have a different pathological picture. Askanazy (1898) and Adams, Denny-Brown and Pearson (1953) reported infiltration of rows of fat cells between muscular bundles and fibres, with atrophy of some fibres.

The cases also illustrate the diversity of thyroid diseases which may produce muscular manifestations. Although they were clearly associated with exophthalmic goitre in two cases, the evidence suggested exophthalmic ophthalmoplegia in another ; and in the other, with clinical evidence of thyrotoxicosis, microscopic examination of the gland revealed chronic thyroiditis.

SUMMARY

Attacks of severe weakness of the lower limbs after sitting were described by four patients. Each patient was unaware of abnormality until he tried to rise. Each would use his arms in attempting to rise, although in severer attacks weakness of the arms and of the grip of the hands might occur. Each patient fell over when he attempted to walk, but found that if he kept his knees straight he was able to remain erect. The severity of the weakness was proportional to the duration of sitting. In some patients other evidence of thyrotoxic muscular disorder was present. In all cases the thyroid gland was implicated. In three cases there was clear evidence of thyrotoxicosis, and the muscular symptoms disappeared after thyroidectomy. The same muscular symptomatology occurs in family periodic paralysis.

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A BIOPSY STUDY OF THE KIDNEY IN DIABETES MELLITUS[1]

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THE discovery of insulin by Banting and Best (1922), and its subsequent therapeutic use changed the natural history of *diabetes mellitus* in clinical practice. Whilst Futcher (1907) found in 1907 that death was due to diabetic coma in 51% of 464 fatal cases of *diabetes mellitus*, Nabarro *et alii* (1952) recently reported 58 cases of diabetic ketosis with only one death, and in none of the 67 fatal cases of Lundbaek (1953) did death occur in diabetic coma. This reduction in the mortality from diabetic coma has had widespread medical, social and genetic consequences. The life expectancy of the diabetic patient has increased, the mortality of diabetic mothers and their children has decreased (Skipper, 1933; Lawrence and Oakley, 1942), and the number of diabetics in the population has progressively increased (Spiegelman and Marks, 1946; Joslin, 1949; Downie, 1951; Tunbridge, 1953).

These actuarial changes have led to increased interest by physicians and pathologists in the complications of *diabetes mellitus*, which now largely determine the prognosis of the diabetic patient.

In young diabetics, cardio-vascular and renal lesions are of special importance. In 1907 Futcher dismissed diabetic renal disease in two lines; in 1953 Strom wrote the "nephropathies finally convict the young diabetic", and a rapidly growing literature testifies to the general agreement of physicians with this statement (Dolger, 1947; Lawrence, 1953). In older diabetics, vascular disease is also the major factor in prognosis (Lundbaek, 1953; Poole, 1953).

Many papers on diabetic renal disease have been published since the classical work of Kimmelstiel and Wilson (1936), and several reviews of the subject have appeared recently (Laipply *et alii*, 1944; Kimmelstiel and Porter, 1948; Allen, 1951; Hall, 1952*a*; Aarseth, 1953). The concept has gradually been evolved of a specific diabetic nephropathy—the Kimmelstiel-Wilson syndrome—in addition to the other vascular and infective changes found in the kidneys of diabetics (Newberger and Peters, 1939). The Kimmelstiel-Wilson syndrome comprises the tetrad of *diabetes mellitus*, nephrotic œdema, albuminuria and hypertension. Many other changes have been associated with these, including retinopathy (Ballantyne and Loewenstein, 1943; Wagener, 1953), decreasing insulin requirements (Zubrod *et alii*, 1951; Dana *et alii*, 1951), peripheral neuropathy (Gilliland, 1951), inversion of the albumin-globulin ratio, the presence of doubly refractile bodies in the urine (Rifkin *et alii*, 1948), and possibly abnormalities of electrolyte metabolism (James *et alii*, 1953). The syndrome is rare, but is found more commonly in females than in males, and in elderly patients. The prognosis is poor.

There has often been a failure to distinguish between the clinical Kimmelstiel-Wilson syndrome and the pathological Kimmelstiel-Wilson lesions in the kidney. Neither the pathological basis of the clinical entity, nor the clinical manifestations of the renal lesions are at all firmly established.

Studies of the kidney in *diabetes mellitus* have been restricted in the past in several respects. Functional studies show changes only late in the disease, and these do not differ from those seen in advanced nephropathy from other causes (Hogeman, 1948; Robertson *et alii*, 1951). Morbid anatomical studies, except in rare instances (Derow and Schlesinger, 1949; Allen, 1951; Astudillo *et alii*, 1952) have been made only on autopsy material, and clinical correlation has been of necessity retrospective and possible only in the late stages of the disease. Neither has it been possible to follow serially the changes seen in individual patients.

In an attempt to overcome these difficulties, a biopsy study has been made of the kidney in *diabetes mellitus*, similar to that recently reported from Scandinavia (Brun *et alii*, 1953). This procedure is, of course, open to difficulties of both technique and interpretation, especially to the sampling error inherent in biopsy studies. In the kidney pathological changes are notoriously uneven in their distribution. On

[1] Received on April 30, 1954.

[2] Working with the aid of a grant from the National Health and Medical Research Council of Australia.

TABLE I

The Clinical and Biochemical Findings in the 20 Cases of Diabetes Mellitus

Case Number, Patient's Sex and Age (Years)	Duration of Diabetes (Years)	Type of Diabetes[1]	Insulin Dosage (Units)	Blood Pressure (Millimetres of Mercury; Systolic/Diastolic)	Retinopathy	Vascular Disease	Albuminuria	Pyuria	Blood Urea Content (Milligrammes per 100 Millilitres)	Maximum Urea Concentration (Grammes *per Centum*)	Total Urea Excretion (Grammes)	Urea Clearance (Van Slyke) (*Per Centum*)	Findings on Intravenous Pyelography	Total Serum Protein Content (Grammes *per Centum*)	Serum Albumin Content (Grammes *per Centum*)	Serum Globulin Content (Grammes *per Centum*)	Serum Cholesterol Content (Milligrammes per 100 Millilitres)	Serum Lipide Content (Milligrammes per 100 Millilitres)	Control of Diabetes
1 F. 52	15	Old	160 RI[2] twice daily	205/105	Diabetic	Congestive cardiac failure. Palpable peripheral vessels	++	Nil	33	2·3	6·3	100	Normal	7·0	5·5	1·5	190	—	Fair
2 F. 67	15	Old	RI 40 a.m. 24 p.m.	240/120	Diabetic	Congestive cardiac failure. Hemiplegia	+	Present: *B. coli* cultured	60–110	—	—	—	Poor dye excretion	6·7	4·3	2·4	—	—	Fair
3 M. 37	21	Young	NPH[3] 48 RI 16 a.m.; NPH 12 p.m.	120/80	Diabetic	Nil	Nil	Nil	26	2·2	6·9	140	Normal	—	—	—	200	—	Poor
4 M. 27	19	Young	NPH 100 RI 16 a.m.	150/80	Diabetic	Nil	+	Nil	44	3·3	5·8	130	Normal	—	—	—	—	—	Poor
5 F. 71	10	Old	PZ[2] 20 RI 16 a.m.	205/80	—	Congestive cardiac failure. Palpable peripheral vessels	++	Present: *B. coli* cultured	64	2·2	3·4	38	Poor dye excretion	6·7	4·2	2·5	234	490	Fair
6 M. 39	18	Young	RI 40 a.m. 32 p.m.	180/110	Diabetic	Nil	++	Present: sterile	62	3·5	6·0	44	Poor dye excretion	5·8	4·1	1·7	360	660	Fair
7 F. 63	10	Old	PZ 32 a.m.	240/100	Diabetic	Cardiac enlargement. Palpable peripheral vessels	++	Nil	70	1·8	4·2	35	Impaired dye excretion	7·2	4·5	2·7	146	460	Fair
8 F. 54	4	Old	PZ 32 RI 16 a.m.	210/120	Diabetic	Cardiac enlargement. Palpable peripheral vessels	+	Nil	54	3·2	7·9	90	Normal	6·8	4·0	2·8	208	525	Good
9 M. 47	—	Old	Nil	140/70	—	Palpable peripheral vessels	Nil	Present: sterile	42	3·73	4·8	—	Normal	6·8	3·1	3·7	—	—	—
10 F. 53	23	Old	PZ 36 RI 20 a.m.	170/80	Diabetic	Claudication	Nil	Present: sterile	40	3·2	8·9	140	—	7·0	4·2	2.8	210	580	Poor
11 F. 16	8	Young	Lente 64 Semi-Lente 32 a.m.	120/80	Nil	Nil	Nil	Present: sterile	15	4·3	9·4	180	—	7·5	4·5	3·0	244	580	Poor
F. 19			RI 12 a.m.	85															
13 M.	11	Young	PZ 40 RI 20 a.m.	180/105	Diabetic	Nil	+	Present: sterile	43	3·1	9·2	95	Impaired dye excretion	7·0	5·2	1·8	220	610	Fair

13 M. 33	11	Young	PZ 40 / RI 20 } a.m.	180/105	Diabetic	Nil	+	Present : sterile	43	3·1	9·2	95	Impaired dye excretion	7·0	5·2	1·8	220	610	Fair
14 M. 53	8	Old	Nil	215/110	Diabetic	Congestive cardiac failure. Bilateral amputation of legs for gangrene	++	Nil	39	2·9	6·0	72	Normal	—	—	—	—	—	Good
15 M. 25	14	Young	PZ 40 / RI 56 } a.m.	140/100	Nil	Nil	Nil	Nil	46	2·4	9·3	267	—	7·7	5·5	2·2	135	—	Poor
16 M. 14	½	Young	PZ 72 / RI 56 } a.m.	130/90	Nil	Nil	Nil	Nil	15	3·7	7·1	300	Poor and delayed dye excretion	6·2	4·3	1·9	230	640	Poor
17 F. 15	1½	Young	PZ 96 / RI 41 } a.m.	120/80	Nil	Nil	Nil	Nil	39	1·4	6·6	98	Normal	7·5	5·0	2·5	182	—	Fair
18 F. 65	5	Old	NPH 8	260/150	Hyper-tensive	Palpable peripheral vessels	Nil	Nil	100	2·8	7·4	117	Normal	6·6	2·8	3·8	240	620	Fair
19 F. 54	19	Old	RI 48 twice a day	150/80	Nil	Nil	Nil	Present : sterile	51	2·2	6·2	210	—	6·5	4·6	1·9	175	—	Fair
20 M. 33	1	Old	PZ 32 / RI 28 } a.m.	140/90	Nil	Nil	Nil	—	27	2·9	8·5	104	Normal	7·6	4·1	3·5	560	2200	Good

[1] Types described by Bornstein and Lawrence (1951).
[2] RI, regular insulin ; PZ, protamine zinc insulin ; NPH, isophane insulin.

the other hand, it has several advantages. It allows detection of early renal lesions before functional impairment is gross, and permits the changes to be followed serially as the disease process evolves, with at all stages a close correlation of clinical and pathological findings.

It may also permit a study of some aspects of the general metabolic disorder in *diabetes mellitus*, which appears in a florid form in the vascular bed of the kidney.

This paper reports the clinical, biochemical and pathological findings in 20 cases of *diabetes mellitus* in which a successful renal biopsy was made, presenting evidence that aspiration biopsy of the kidney is a valuable tool in the study of diabetic renal disease, and more generally, of the vascular complications of *diabetes mellitus*.

MATERIAL AND METHODS

Twenty cases of *diabetes mellitus* have been studied. In all a detailed history was taken and a full clinical examination made. In some, additional case records were available going back as far as twenty-one years.

The biochemical tests made were estimations of blood urea, total serum protein, serum albumin and globulin, blood sugar and fasting serum cholesterol and total serum lipides (Kunkel *et alii*, 1948). The urine was examined macroscopically, chemically for protein, reducing substances, keto-acids and urea, and microscopically for casts, erythrocytes, pus cells and organisms. Bacteriological cultures were made when indicated by the clinical or other laboratory findings. Renal function was assessed by intravenous pyelography and by urea clearance and concentration-excretion tests (Maxwell, 1944).

A renal biopsy was performed in all patients. In one (Case 18) this was performed during laparotomy for another cause; in the others material was obtained by aspiration biopsy of the right kidney with a Franseen needle under local anæsthesia, after preliminary localization of the kidney by intravenous or retrograde pyelography (Iversen and Brun, 1951 ; Joske, 1954). No complications of biopsy occurred and none of the patients had macroscopically evident hæmaturia after biopsy. The biopsy material was fixed immediately in 10% formol saline solution, and sections were stained with hæmatoxylin and eosin, with van Gieson's connective tissue stain, and in some cases by the periodic acid-Schiff method.

In a few cases other histological material was available for examination. This included liver tissue obtained by aspiration biopsy (King and

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8 F. 54	4	Old	PZ 32 RI 16 } a.m.	210/ 120	Diabetic	Cardiac enlargement. Palpable peripheral vessels	+	Nil	54	3·2	7·9	90	Normal	6·8	4·0	2·8	208	525	Good
9 M. 47	—	Old	Nil	140/ 70	—	Palpable peripheral vessels	Nil	Present: sterile	42	3·73	4·8	—	Normal	6·8	3·1	3·7	—	—	—
10 F. 53	23	Old	PZ 36 RI 20 } a.m.	170/ 80	Diabetic	Claudication	Nil	Present: sterile	40	3·2	8·9	140	—	7·0	4·2	2.8	210	580	Poor
11 F. 16	8	Young	Lente 64 Semi-Lente 32 } a.m.	120/ 80	Nil	Nil	Nil	Present: sterile	15	4·3	9·4	180	—	7·5	4·5	3·0	244	580	Poor
12 F. 19	7	Young	NPH 64 RI 12 } a.m.	135/ 85	Nil	Nil	Nil	Present: sterile	—	—	—	—	Normal	7·0	4·2	2·5	216	520	Poor
13 F. [illegible]	11	Young	PZ 40 [illegible] } a.m.	180/ [illegible]	Diabetic	Nil	+	Present: sterile	43	3·1	9·2	95	Impaired dye ex-	7·0	5·2	1·8	220	610	Fair

12 F. 19																							
13 M. 33	11	Young	PZ RI	40 20 } a.m.	180/ 105	Diabetic	Nil	+	Present: sterile	43	3·1	9·2	95	Impaired dye excretion	7·0	4·2	2·5	216	3500	Poor			
14 M. 53	8	Old	Nil		215/ 110	Diabetic	Congestive cardiac failure. Bilateral amputation of legs for gangrene	++	Nil	39	2·9	6·0	72	Normal	—	—	—	—	—	Good			
15 M. 25	14	Young	PZ RI	40 56 } a.m.	140/ 100	Nil	Nil	Nil	Nil	46	2·4	9·3	267	—	7·7	5·5	2·2	135	—	Poor			
16 M. 14	¾	Young	PZ RI	72 56 } a.m.	130/ 90	Nil	Nil	Nil	Nil	15	3·7	7·1	300	Poor and delayed dye excretion	6·2	4·3	1·9	230	640	Poor			
17 F. 15	1¼	Young	PZ RI	96 41 } a.m.	120/ 80	Nil	Nil	Nil	Nil	39	1·4	6·6	98	Normal	7·5	5·0	2·5	182	—	Fair			
18 F. 65	5	Old	NPH	8	260/ 150	Hypertensive	Palpable peripheral vessels	Nil	Nil	100	2·8	7·4	117	Normal	6·6	2·8	3·8	240	620	Fair			
19 F. 54	19	Old	RI	48 twice a day	150/ 80	Nil	Nil	Nil	Present: sterile	51	2·2	6·2	210	—	6·5	4·6	1·9	175	—	Fair			
20 M. 33	1	Old	PZ RI	32 28 } a.m.	140/ 90	Nil	Nil	Nil	—	27	2·9	8·5	104	Normal	7·6	4·1	3·5	360	2200	Good			

[1] Types described by Bornstein and Lawrence (1951).
[2] RI, regular insulin; PZ, protamine zinc insulin; NPH, isophane insulin.

the other hand, it has several advantages. It allows detection of early renal lesions before functional impairment is gross, and permits the changes to be followed serially as the disease process evolves, with at all stages a close correlation of clinical and pathological findings.

It may also permit a study of some aspects of the general metabolic disorder in *diabetes mellitus*, which appears in a florid form in the vascular bed of the kidney.

This paper reports the clinical, biochemical and pathological findings in 20 cases of *diabetes mellitus* in which a successful renal biopsy was made, presenting evidence that aspiration biopsy of the kidney is a valuable tool in the study of diabetic renal disease, and more generally, of the vascular complications of *diabetes mellitus*.

MATERIAL AND METHODS

Twenty cases of *diabetes mellitus* have been studied. In all a detailed history was taken and a full clinical examination made. In some, additional case records were available going back as far as twenty-one years.

The biochemical tests made were estimations of blood urea, total serum protein, serum albumin and globulin, blood sugar and fasting serum cholesterol and total serum lipides (Kunkel *et alii*, 1948). The urine was examined macroscopically, chemically for protein, reducing substances, keto-acids and urea, and microscopically for casts, erythrocytes, pus cells and organisms. Bacteriological cultures were made when indicated by the clinical or other laboratory findings. Renal function was assessed by intravenous pyelography and by urea clearance and concentration-excretion tests (Maxwell, 1944).

A renal biopsy was performed in all patients. In one (Case 18) this was performed during laparotomy for another cause; in the others material was obtained by aspiration biopsy of the right kidney with a Franseen needle under local anæsthesia, after preliminary localization of the kidney by intravenous or retrograde pyelography (Iversen and Brun, 1951; Joske, 1954). No complications of biopsy occurred and none of the patients had macroscopically evident hæmaturia after biopsy. The biopsy material was fixed immediately in 10% formol saline solution, and sections were stained with hæmatoxylin and eosin, with van Gieson's connective tissue stain, and in some cases by the periodic acid-Schiff method.

In a few cases other histological material was available for examination. This included liver tissue obtained by aspiration biopsy (King and

Perry, 1948), and muscle biopsies from the *pectoralis major* or the long flexor muscles of the forearm. A complete post-mortem examination was performed on one patient who died (Case 14).

RESULTS

The 20 patients studied showed most of the clinical features seen in the different types of *diabetes mellitus*, including those generally considered significant in the development of the various pathological changes in the kidney. The clinical and biochemical findings in these patients are recorded in Table I.

Clinical Features

There were nine male and 11 female patients, and their ages ranged from fourteen to seventy-one years. The age of onset of *diabetes mellitus* varied from the first to the seventh decade, and the duration of the diabetes, from the time of detection, from a few weeks to twenty-three years.

Nine of the patients were considered on clinical grounds to be " young diabetics without available plasma insulin ", and 11 to be " older diabetics with available plasma insulin " as described by Bornstein and Lawrence (1951), although plasma insulin assays were not performed. The insulin requirements at the time of investigation varied from zero to 320 units daily. Only one patient (Case 14) showed a progressive decrease in insulin requirements while under observation.

The complete clinical picture of the Kimmelstiel-Wilson syndrome was not seen.

Hypertension (systolic blood pressure over 140 millimetres of mercury, or diastolic blood pressure over 100 millimetres of mercury) was present in 12 patients, but in five of these (Cases 4, 5, 7, 10, 19) only the systolic blood pressure was elevated. In two (Cases 13 and 18) a sedation test with " Sodium Amytal " showed the blood pressure to be labile. All grades of diabetic retinopathy were seen—hæmorrhage and exudates, new vessel formation and micro-aneurysms being observed; three patients had cataract. In one patient (Case 18) hypertensive changes only were observed, and in seven the *fundi oculorum* were normal.

Evidence of vascular disease was present in nine patients, eight of whom had palpable thickening of peripheral arteries, and in three of these calcification of the larger arteries was demonstrated radiologically. One patient (Case 10) had claudication, another (Case 14) had had a leg amputated for gangrene, and a third (Case 2) suffered from arteriosclerotic Parkinsonism and later hemiplegia. Congestive cardiac failure was present in four patients (Cases 1, 2, 5 and 14).

One patient (Case 9) had tertiary syphilis with hepatic cirrhosis, confirmed by liver biopsy.

Albuminuria, ranging in amount from a trace to " +++ ", was present in nine cases, being persistent and severe in five (Cases 1, 5, 6, 7 and 14). Granular and hyaline casts were occasionally noted. Pyuria occurred in nine cases, and *Bacterium coli* was cultured from the urine in two instances (Cases 2 and 5), and in another (Case 14) *Staphylococcus aureus* and *Pseudomonas pyocyanea*.

Biochemical Findings

It was not possible to give any general assessment of renal function from the techniques used, although in 11 instances the blood urea was over 40 milligrammes per 100 mils and in Case 2 it reached 110 milligrammes per 100 mils. Clinical " uræmia " did not occur. The total serum protein was below 6·0 grammes *per centum* in only one case (Case 6—5·8 grammes *per centum*); and inversion of the albumin-globulin ratio occurred in only two cases (Cases 9 and 18). In Case 9 this was associated with *cirrhosis hepatis*. The serum cholesterol exceeded 200 milligrammes per 100 mils in 10 of 17 cases in which it was estimated, being above 300 milligrammes per 100 mils in two (Case 6, 360 milligrammes per 100 mils; Case 20, 560 milligrammes per 100 mils). The fasting serum lipides were estimated in 11 instances, and found to be above 650 milligrammes per 100 mils in the same two cases (Case 6, 660 milligrammes per 100 mils; Case 20, 2200 milligrammes per 100 mils).

Control of Diabetes Mellitus

The control of the diabetes in this series, as indeed in any group of diabetics, is difficult to assess. These patients have all been observed in the wards and in the out-patient department, and control has been assessed as follows: " good " if random blood sugar estimations have given satisfactory findings and if glycosuria has been found rarely; " fair " if blood and urine sugar contents have not been satisfactory, but if there has been no ketosis and the patient remains in good health; and " poor " if, in addition to hyperglycæmia and glycosuria, ketosis has occurred as the result of the failure of the patient to honour his obligations in regard to diet and insulin (ketosis due to intercurrent infection is not included). Control

TABLE II

The Histological Changes Seen in 20 Successful Renal Biopsies Performed on Diabetic Patients.[1]

Case Number	Patient's Age (Years)	Sex	Total Number of Glomeruli	Normal Glomeruli	Diffuse Type Glomeruli	Nodular Type Glomeruli	Exudative Type Glomeruli	Sclerosed Glomeruli	Juxtaglomerular Arterioles	Small Arteries	Tubules	Interstitial Tissue
1	52	F.	9	9	—	—	—	—	Very slight hyaline change	—	Normal	Very occasional lymphocytes
2	67	F.	32	2	24	2	—	5	Moderate hyaline change	Normal	Occasional hyaline cast	Normal
3	37	M.	12	11	—	—	—	1	Very occasional hyaline change	Normal	Normal	Normal
4	28	M.	30	27	Slight in 5	—	2	1	Many, severe hyaline change	Normal	Normal	Normal
5	65	F.	24	—	7	3	5	9	Many, severe hyaline change	Moderate intimal thickening	Many hyaline casts, considerable tubular atrophy	Considerable fibrosis
6	39	M.	17	1	6	—	6	6 (2 still showed exudate)	Many, moderately severe hyaline change	Normal	Occasional hyaline casts, moderate atrophy	Considerable fibrosis and lymphocyte infiltration
7	63	F.	24	—	4	14	9	2	Many, severe hyaline change	Considerable intimal thickening	Many hyaline casts	Moderate fibrosis and occasional lymphocytes
8	53	F.	16	7	Slight in 2	1	1	5	Many, severe hyaline change	Slight medial thickening	Occasional hyaline and granular casts	Slight fibrosis and lymphocyte infiltration
9	47	M.	8	6	Slight in 2	—	—	—	Normal.	Normal.	Normal.	Normal
10	53	F.	5	—	Slight in 5	—	—	—	Slight hyaline change	Normal	Occasional hyaline casts	Slight patchy fibrosis
11	16	F.	19	19	—	—	—	—	Normal	Normal	Normal	Normal
12	19	F.	8	8	—	—	—	—	Normal	Normal	Normal	Normal
13	33	M.	15	12	Slight in 2	—	—	1	Occasional moderate hyaline change	—	Normal	Slight patchy fibrosis
14	53	M.	3	—	Slight in 3	—	—	—	Occasional slight hyaline change	—	Occasional hyaline casts	Normal
15	25	M.	18	18	—	—	—	—	Very occasional hyaline nodule	Normal	Normal	Normal
16	14	M.	14	8	In 6 otherwise normal glomeruli the capsular epithelium surrounding the neck was tall columnar in type				Normal	Normal	Normal	Normal
17	14	F.	18	18	—	—	—	—	Normal	Normal	Normal	Normal
18	60	F.	24	13	Slight in 3	—	—	8	Occasional hyaline change, 1 "onion-skin" arteriole	Normal	Slight atrophy	Slight patchy fibrosis
19	53	F.	10	7	—	—	—	3	Occasional very slight hyaline change	Normal	Normal	Very slight patchy fibrosis
20	34	M.	25	25	—	—	—	—	Normal	Normal	Normal	Normal

[1] Since some glomeruli showed more than one type of change these have been recorded more than once in the table.

was assessed as "good" in three, "fair" in nine and "poor" in seven cases. In one case (Case 9) insufficient time had elapsed since the detection of *diabetes mellitus* to determine the efficiency of control.

Biopsy Findings

The histological findings in the kidney are recorded in Table II. The amount of renal cortex obtained in each biopsy is indicated by the number of glomeruli included. This varied from three to 33 glomeruli, with an average of 16. The principal changes noted were in the glomeruli and the blood vessels; an attempt has been made to estimate the extent, type and severity of these changes.

The glomeruli showed several types of abnormality. The least conspicuous change was an increase of acidophilic material between the tuft capillaries, which themselves remained normally patent. Where this was slight and patchy it was considered to be within normal limits.

When the acidophilic material was more profuse, it resembled the diffuse changes described by Bell (1950) as characteristic of diabetes. Such material either may have been deposited in between the capillary basement membranes, or may have been an actual thickening of the basement membranes; glomeruli affected in this way are recorded in the table as "diffuse type glomeruli" (Figures I and II). An apparent transition was noted from this form to the more usually described nodular intercapillary lesion (Kimmelstiel and Wilson, 1936), in which material with generally similar staining properties is found in wider and often rounded masses in one or more capillary tufts,

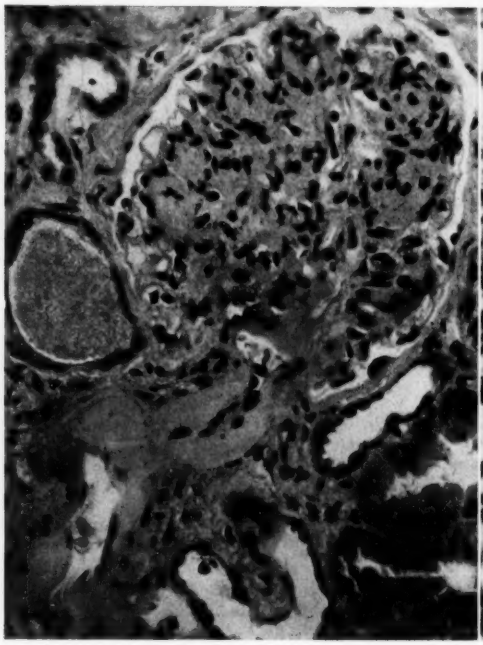

FIGURE I

Renal tissue obtained by needle biopsy from a female patient, aged sixty-seven years (Case 2), who had had well-controlled diabetes for fifteen years. There is a diffuse increase of intercapillary material which has largely obliterated the capillary lumina ("diffuse type glomerulus"). The wall of the juxtaglomerular arteriole is grossly thickened and replaced by hyaline material. (Weigert and van Gieson stain. ×350.)

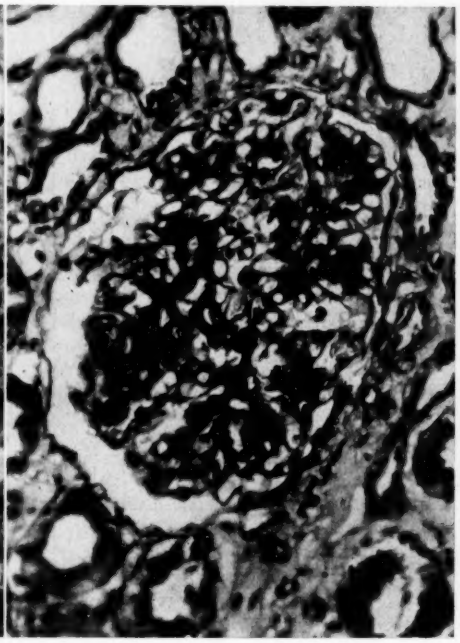

FIGURE II

Renal biopsy from the same patient as Figure I (Case 2). This shows another glomerulus in which the diffuse changes present are tending to become nodular ("diffuse type glomerulus"). The intercapillary material is "P.A.S. positive". (Periodic acid Schiff stain. ×350)

often lying centrally and surrounded by a still patent capillary. Such glomeruli are recorded as "nodular type glomeruli" (Figures III and IV). Glomeruli were also seen in which hyaline, slightly more translucent material was noted in masses replacing portion of a tuft, or adjacent and external to a tuft capillary, or in other instances attached to or covered by capsular epithelium. These changes resemble the capsular lesions described by Kimmelstiel and Wilson (1936), the "fibrin cap" and "capsular drop" lesions described by Barrie *et alii* (1952), and the hyaline-fibrinoid lesion described by Koss (1952), and have been recorded by us as "exudative type glomeruli" (Figures IV, V and VI). Occasional glomeruli were also seen in which the whole glomerulus was converted into a fibrous ball in which little detail could be distinguished; in most cases these were identical with the sclerosed glomeruli resulting from ischæmia and found in senile nephrosclerosis, but in others nodular or exudative lesions could still be seen as part of the fibrosed glomerulus (Figure IV). These sclerosed glomeruli are also recorded in Table II.

The vascular changes have been listed separately under "juxtaglomerular arterioles" and "small arteries". The juxtaglomerular arterioles refer to both afferent and efferent glomerular arterioles, and no attempt has been made to distinguish between them. Except in one instance (Case 18) in which an arteriole showed a laminated "onionskin" appearance, the changes noted were those of hyaline thickening of the arteriolar wall, which encroached upon the lumen and in extreme cases resulted in almost complete occlusion (Figures I and V). This hyaline material showed similar staining properties to the "exudative type" lesions, and often resembled an intravascular or intramural deposit. The arterial appearances could not be recorded in

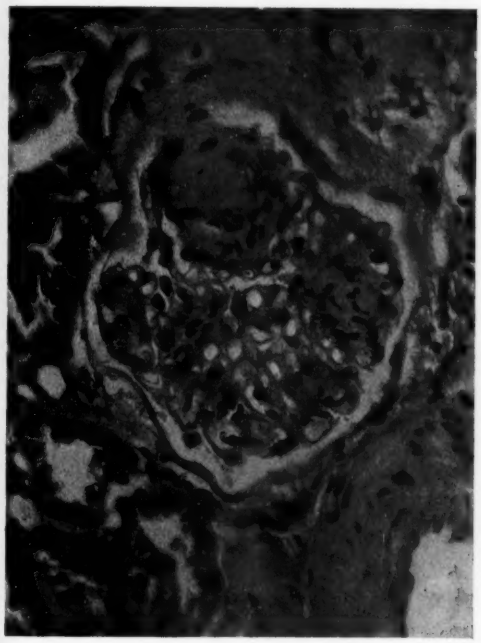

Figure III

Renal biopsy obtained from a female diabetic patient, aged sixty-three years (Case 7). In this glomerulus the lesions are more nodular, the largest having a typically pale hyaline centre ("Nodular type glomerulus"). (Weigert and van Gieson stain. ×350)

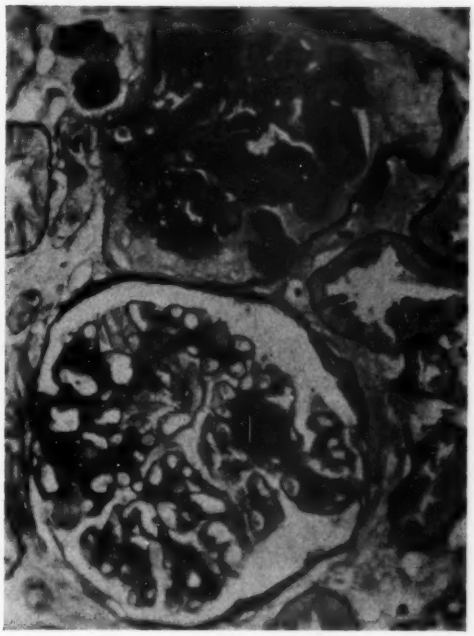

Figure IV

Renal biopsy from the same patient as Figure III (Case 7). The lower glomerulus shows diffuse intercapillary changes with a larger nodular lesion in one area. The upper glomerulus is ischæmic; in it can be seen folded, wrinkled capillary basement membranes, and also globules of hyaline material at the tips of the tufts. This is an ischæmic "exudative type glomerulus". (Periodic acid Schiff stain. ×350)

all cases, as arteries were occasionally not seen in the biopsy material. The changes seen were occasional subintimal deposits of hyaline material or more severe intimal thickening.

The changes in the tubules were not gross. In some instances they were reduced in number, but a conspicuous feature was the presence of hyaline and granular casts, which were very numerous in two biopsy specimens (Cases 5 and 7). Patchy interstitial fibrosis and infiltration with lymphocytes were also occasionally noted.

When changes from the normal were found, sections were stained by Schiff's periodic acid stain, light green and picric acid being used as counterstain. By this method the basement membranes of capillaries and tubules are clearly shown, and the diffuse, nodular and exudative lesions and the vascular changes are well demonstrated (Figures II and IV). There were slight but distinct differences between the staining properties of these structures; normal basement membranes, the diffuse type of glomerular change and the smaller nodules stained a deep red, while the larger nodules, the exudative lesions of the tufts and capsules and the hyaline juxtaglomerular arterioles stained an orange-red colour. These staining reactions confirmed the opinions gained from the study of post-mortem material that the nodular lesions developed from the diffuse lesions by the deposition in the intercapillary area of hyaline glycoprotein material of similar type to that deposited in the exudative lesions and in the arterioles.

In five of the 20 biopsy specimens the pathological changes were considerable; the remainder showed minimal changes or were

FIGURE V

Renal biopsy obtained from a diabetic male, aged thirty-nine years (Case 6). The glomerulus shows slight diffuse intercapillary change and at the top of the figure there is exudate uniting the tip of a tuft to similar material lining the capsule. A deposit of this exudate can be seen beneath the capsular epithelium over a large area at the top, and as a more discrete globule beneath the epithelium at the lower pole ("exudative type glomerulus"). A thickened, hyalinized juxtaglomerular arteriole is seen at the lower left of the glomerulus. (Weigert and van Gieson stain. ×350)

FIGURE VI

Renal biopsy, also from Case 6. This glomerulus shows a well defined exudative lesion on the surface of a tuft in the lower right hand portion of the figure. The remainder of the glomerulus shows moderate diffuse changes—ischæmic change is not yet marked ("diffuse" and "exudative type glomerulus"). (Weigert and van Gieson stain. ×350)

within normal limits. In three specimens (Cases 5, 6 and 7) the glomerular changes were gross, only one normal glomerulus being seen. Together these specimens showed all the described forms of diabetic glomerulosclerosis.

In one biopsy specimen (Case 16) the only significant finding was the presence of cuboidal or columnar epithelium in the capsule of several otherwise normal glomeruli in place of the normal flattened epithelium. A similar appearance has since been seen in two further renal biopsy specimens from young diabetic patients.

Other material examined included that obtained by muscle biopsies (Cases 6 and 14), which showed no abnormality, and by liver biopsy (Case 9), which revealed the presence of moderately severe cirrhosis. One patient (Case 14) died eighteen days after amputation of a leg for gangrene, and an autopsy was performed. Histological examination of the kidneys revealed similar arteriolar and diffuse glomerular changes to those seen in the renal biopsy specimen obtained five months previously. In addition occasional nodular and exudative glomerular lesions were seen which had not been noted in the renal biopsy specimen, probably since it had included only three glomeruli.

Correlation of Clinical and Biopsy Findings

An attempt was made to correlate significant clinical findings with the histological appearance found in the biopsy specimens.

Age and Distribution of Disease.—Pathological changes were present in biopsy specimens from both "young" and "old" diabetics, but the changes were generally more severe in the latter group, as reported by other authors (Laipply *et alii*, 1944; Bell, 1950; Hall, 1952*a*). When changes were observed in specimens from "young" diabetics, the known duration of *diabetes mellitus* was longer than in "old" diabetics with corresponding changes. However, nodular glomerular lesions were not observed in "young" diabetics, but only in the older group, whereas exudative lesions were found in both types of patient. It is noteworthy that normal biopsy findings were observed in "old" and "young" patients, the duration of whose disease was fourteen, twenty-one, fifteen and nineteen years respectively, although there is a frequently described relation between duration of *diabetes mellitus* and glomerulosclerosis (Goodof, 1945; Henderson *et alii*, 1947; Zins, 1949).

Sex.—The predominance of renal lesions in female patients observed elsewhere (Siegal and Allan, 1941; Henderson *et alii*, 1947; Platt and Davson, 1950; Hall, 1952*a*) was also found in this series, cognizance being taken of the duration of disease. Gross changes were present in biopsy specimens from four of 11 female, and only one from nine male patients.

Blood Pressure.—All 12 patients with systolic hypertension showed renal changes. In all but two of these arteriolosclerosis was present; all had glomerular changes. In seven instances there was also diastolic hypertension, but no significant increase in the severity of the renal lesions was observed. Very gross changes were seen in patients with and without diastolic hypertension. One patient whose blood pressure was 260 millimetres of mercury, systolic, and 150 millimetres, diastolic (Case 18), had an "onionskin" appearance in a juxtaglomerular arteriole.

In the eight patients with normal blood pressures the renal biopsy findings were within normal limits, except for one (Case 9) with minimal diffuse glomerular changes.

Retinal Changes.—Ophthalmoscopic examination of the *fundi oculorum* at the time of renal biopsy was made in 18 cases. Abnormal appearances were observed in 11 instances. Two of these 11 patients had extensive retinopathy of diabetic type in the absence of demonstrable changes in the renal biopsy material. In one patient (Case 18) the retinopathy was hypertensive in type. This case has been referred to above. All the types of renal pathology discussed were met with in the remaining eight patients.

Of the seven patients without retinopathy, the biopsy appearances were normal in all except one who had occasional sclerosed glomeruli and slight arteriolar thickening (Case 19).

This correlation of retinal and renal pathology has been observed elsewhere (Ballantyne and Loewenstein, 1943; Ashton, 1949; Wagener, 1953).

Systemic Vascular Disease.—In all but one of the patients with systemic vascular disease, biopsy revealed abnormalities in the kidney. In those without systemic vascular disease the lesions were much less frequent, and the biopsy findings were normal in seven of 11 instances. However, considerable change was present in two of these (Cases 4 and 6).

In Case 9, in which tertiary syphilis was also present, only slight diffuse glomerular changes were present.

Proteinuria.—There was a general correlation between the extent of the change found in biopsy specimens and the degree of proteinuria. All patients with advanced renal involvement had gross proteinuria, but moderate proteinuria was also present in two patients without histologically evident abnormality. One of the latter had congestive cardiac failure. In those without albuminuria renal changes were absent or minimal. Patients with slight albuminuria showed a gradation from the normal to moderately severe renal abnormalities.

Pyuria.—Nine patients had pyuria, but there were no corresponding changes in histological findings in the kidneys.

Renal Function.—Since no definitive assessment of renal function was made, no correlation of renal function and histological appearances was possible. By the use of clearance tests renal function has been assessed before death, but with no correlation with post-mortem findings (Hogeman, 1948; Corcoran *et alii*, 1948; Robertson *et alii*, 1951).

Serum Proteins. — Hypoproteinæmia was present in one patient (Case 6), with gross albuminuria. This patient had extensive renal damage.

Hypercholesterolæmia and Hyperlipæmia.—One of the two patients with hypercholesterolæmia and hyperlipæmia had gross renal disease; the other, with essential hyperlipæmia, showed no renal changes.

Control.—There was no correlation whatsoever between the degree of control of hyperglycæmia and glycosuria and the occurrence of renal abnormalities. Some patients with good control showed extensive renal disease, and some with poor control showed no histological changes.

Discussion

In this series of 20 cases of *diabetes mellitus*, aspiration biopsy of the kidney has revealed all the recorded types of histological change of diabetic glomerulosclerosis, as well as other vascular changes. These findings in the living patient have been available for comparison and correlation with the results of clinical and biochemical investigations.

Despite world-wide intensive study of *diabetes mellitus*, the fundamental nature of the condition is still not clearly understood. There is considerable recent evidence that it is itself a clinical syndrome resulting from a variety of causes, and not a single disease process (Himsworth, 1949; Lawrence, 1951; Bornstein and Lawrence, 1951).

The understanding of the natural history of *diabetes mellitus* requires a study of all the progressive changes in the tissues and the factors influencing their development. Our experience with renal biopsy leads us to believe that the kidney is in many instances affected early and severely, and may reflect in more gross form many of the changes widespread in the rest of the body.

Most emphasis in the literature on "diabetic nephropathy" has been laid on the various aspects of diabetic glomerulosclerosis and the Kimmelstiel-Wilson syndrome, although some authors have indicated that diabetic nephropathy is not a single disease entity and have stressed the roles of "degenerative", "hypertensive" and "infective" processes (Hall, 1952*b*; Baldwin and Root, 1940; John, 1932; Edeiken, 1945).

It may be of value, therefore, to attempt to distinguish the changes which represent part of the diabetic process from those which are secondary manifestations.

The changes seen in the kidney in diabetic patients vary from those also found in non-diabetics, through those found more frequently in diabetes to those thought to be almost pathognomonic of *diabetes mellitus*. The first group includes atherosclerosis, arteriolosclerosis and pyelonephritis; the second group includes the diffuse forms of glomerulosclerosis, thought by Kimmelstiel and Wilson (1936) to represent "an acceleration of the aging process", and the exudative glomerulosclerotic lesions which are also stated to occur in glomerulonephritis (Barrie *et alii*, 1952); the third group includes the nodular glomerulosclerotic lesions.

The predisposition of diabetic patients to infection accounts for the incidence of pyelonephritis and possibly for papillary necrosis of the medulla. However, the other described lesions may be arranged in ascending order of relative frequency in diabetics, culminating in the nodular glomerulosclerotic lesion which occurs almost exclusively in diabetics. It would appear that *diabetes mellitus* is a predisposing factor to or hastens the changes of atherosclerosis and arteriolosclerosis. To an even greater extent it is a predisposing factor in "an acceleration of the aging process", the diffuse glomerulosclerotic lesion. The exudative glomerulosclerotic lesions are more specific to diabetes, but have been stated by Hall (1952*b*) to result from the rapid ischæmia of severe atherosclerosis. This appears unlikely, since portions of single glomerular tufts may be alone affected (Figure VI). On the other hand, exudative lesions of both tufts and

capsule may well be an indication of a more fulminating course of the disease. The nodular glomerulosclerotic lesion, which is accepted by most writers as practically confined to diabetes, histologically resembles a combination of the diffuse and exudative lesions in which the diffuse lesions have been expanded by the deposition in them of exudative material (Figure III).

The nature of these renal changes remains obscure. However, the similarity of staining properties of the arteriolar and exudative lesions and the central areas of the nodular lesions to each other, and the close resemblance in appearance and situation of the glomerular lesions to some forms of amyloidosis (Simon, 1940; Fahr, 1942; Bogliolo, 1946), suggest that a common feature is the deposition of abnormal protein material in certain sites in the kidney. In some cases such material may line endothelial surfaces, in others permeate and replace the vessel walls, while in still others it may accumulate between denser structures. The staining properties of the material suggest that it contains protein, polysaccharide and some lipid. McManus (1950) considered arteriolar hyalin a glycoprotein on histological grounds, and Churg and Grishman (1953) concluded after study by phase microscopy that the hyalin in the glomerular lesions might be "albuminoid substance deposited from the blood and in this respect similar to arteriolar hyalin". A similar concept was invoked for capillary lesions in glomerulonephritis by Rokitansky (1849). Friedenwald (1950) states that the hyalin material lying in or on the capillary walls in the retina and in the renal glomeruli is identical and is a mucopolysaccharide. It may well be relevant therefore that Jacobs (1949) found considerably larger amounts of mucopolysaccharide in the form of glucosamine in the blood of diabetics than in non-diabetics, with the highest values in uncontrolled diabetics. More recently Berkman *et alii* (1953) showed that in diabetic patients with degenerative vascular disease the total polysaccharides bound to the serum proteins and the glucosamine of the serum were increased.

These findings lend support to the contention that in some forms of *diabetes mellitus* there is a generalized metabolic disturbance, which leads ultimately to the widespread deposition in the body of abnormal glycoprotein and lipid material. This type of metabolic change may not necessarily be exclusive to diabetes, but it appears to occur in a florid form in *diabetes mellitus*. The kidney is affected by these changes to a considerable degree, and histological examination of renal tissue may show numerous manifestations of this abnormality. Not all the renal lesions are directly due to this upset, as some splitting and thickening of the glomerular capillary basement membrane may follow ischæmia (Figure IV) or some other factor common to glomerulonephritis (McGregor, 1929; Ellis, 1942; Kimmelstiel and Porter, 1948; Bell, 1953). In all probability the changes in the retina (Ashton, 1949; Wagener, 1953) and the extremities (Meigbow *et alii*, 1953; Mendlowitz *et alii*, 1953) have a similar pathogenesis.

The relation of this postulated metabolic disturbance to hyperglycæmia and its therapeutic control with insulin is of the greatest importance in the prevention and treatment of the vascular complications of *diabetes mellitus*. Although many authors have suggested that control of hyperglycæmia reduces the frequency of complications (Mann *et alii*, 1949; Wilson *et alii*, 1951), there is considerable evidence that control of hyperglycæmia alone does not materially affect the course of diabetic vascular disease (Dolger, 1947; Croom and Scott, 1949; Gilliland, 1951). This is borne out by the present study.

Summary

A biopsy study of the kidney has been made in 20 cases of *diabetes mellitus*; the patients showed between them all the manifestations of diabetic renal disease except nephrotic œdema.

In these cases all the recorded histological features of diabetic nephropathy were demonstrated in the living patient. No complications of renal biopsy were observed, and it is concluded that renal biopsy is a valuable method for the investigation of diabetic renal disease and the other vascular complications of *diabetes mellitus*.

The renal changes demonstrated were atherosclerosis of small arteries, hyaline arteriolosclerosis, and diffuse, nodular and exudative glomerular lesions. The appearances and staining reactions of the hyaline deposits in arterioles, glomerular nodules and glomerular exudates suggest that these are of similar composition, containing glycoprotein.

Abnormal biopsy appearances were more frequent in "old" diabetics, in female patients, and in those with hypertension, retinopathy, systemic vascular disease and proteinuria.

No correlation at all could be found between the control of hyperglycæmia with insulin and the occurrence of renal changes in the biopsy material.

It is suggested that in some diabetic patients there is a metabolic disorder which leads to the

widespread deposition of an abnormal material on and in vessel walls and in adjacent structures. This is apparently not influenced by the effective control of the blood sugar level with insulin.

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STUDIES IN MITRAL STENOSIS

III. THE CLINICAL FEATURES[1]

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The physiological, radiological and electrocardiographic findings in a series of cases of mitral stenosis have been reported in two earlier papers (Blacket *et alii*, 1953; Sinclair-Smith *et alii*, 1953). In the present paper the clinical features in these cases are discussed.

Clinical Material

There were 57 patients (43 females and 14 males), 48 of whom were subsequently submitted to mitral valvotomy. As was described in the first paper of the series, they were grouped into functional classes according to the degree of incapacity caused by their cardiac disease. The classes were denoted as II, III and IV, corresponding broadly with those recommended by the New York Heart Association (1945). Class II included 14 patients who complained of dyspnœa on moderate exertion—for example, hurrying on level ground or climbing several flights of stairs. Class III comprised 26 patients who were dyspnœic on mild effort, such as climbing one flight of stairs or performing the less arduous household tasks. In Class IV were placed the 17 very severely incapacitated patients who were breathless on the slightest effort, some being confined to bed.

The average age for the whole series was thirty-three years, with a range of nineteen to fifty-four years. There was no significant difference between the classes, the mean age in Class II being 31·6 years, in Class III 34·6 years, and in Class IV 33·6 years.

Twenty-two patients (four in Class II, 12 in Class III and six in Class IV) had a definite history of acute rheumatism. A further 10 had a doubtful history. Twenty-four (slightly more than 40% of the total) had no knowledge of preceding rheumatism. An analysis of the case histories showed that there was no relationship between the intensity of the previous rheumatic history and the severity of the chronic valvular disease at the time of study.

[1] Received on June 25, 1954.

Analysis of Clinical Data

The clinical data were analysed as follows: (i) the diagnostic signs of mitral stenosis; (ii) the symptoms and signs resulting from pulmonary hypertension; (iii) clinical evidence of reduced cardiac output; (iv) complications: (*a*) congestive cardiac failure, (*b*) auricular fibrillation, (*c*) subacute bacterial endocarditis and peripheral embolism.

The Diagnostic Signs of Mitral Stenosis

In all patients, mitral stenosis was considered to be the only significant valvular lesion. The criteria for selection were described in the first paper, and included the following: (i) the presence of the classical auscultatory signs at the mitral area; (ii) absence of clinical, radiological or electrocardiographic evidence of left ventricular enlargement; (iii) fluoroscopic evidence of left auricular enlargement. The auscultatory signs at the mitral area were subjected to further analysis, as follows.

Diastolic Murmur and Thrill.—A rumbling mid-diastolic murmur at the mitral area was heard in every patient, and with the exception of two cases in Class III there was presystolic accentuation of the murmur in all patients with sinus rhythm. A diastolic thrill was felt in 36 patients during rest and in a further two after exercise. The intensity of the murmur and the presence of a thrill were found to have no relationship with the magnitude of blood flow through the valve, the mitral valve area, or the pressure gradient across the valve during diastole. There was no difference between the three classes as regards the intensity of the diastolic murmur or the incidence of a diastolic thrill.

Ten patients were found at operation to have a calcified mitral valve. One of these (Case 32) had a very soft murmur and no thrill, while another (Case 35) had an unusually loud murmur and a pronounced thrill. In the remaining eight patients the murmur had no particular differentiating character.

TABLE I

Class II

Case Number	Age (Years)	Sex	Symptoms: Pulmonary Hypertension: Frank Haemoptysis	Acute Episodic Dyspnœa after Effort	Nocturnal Paroxysmal Dyspnœa	Recurrent "Bronchitis"	"Pneumonia and Pleurisy"	Central Chest Pain	Symptoms: Low Cardiac Output: Excessive Fatigue	Low Cardiac Output: Effort Syncope	Congestive Cardiac Failure: Ankle Œdema	Congestive Cardiac Failure: Frank Failure	Clinical Signs: Rhythm	Diagnostic Signs of Mitral Stenosis: Apical Diastolic Murmur	Apical Diastolic Thrill	Accentuated Apical First Heart Sound	Opening Snap	Apical Systolic Murmur[1]	Pulmonary Hypertension: Character of Apex Beat[2]	Right Ventricular Pulsation	Pulmonary Artery Pulsation	Pulmonary Second Sound[3]	Graham Steell Murmur	Low Cardiac Output: Volume of Radial Pulse[4]	Coldness and Cyanosis of Extremities	X-Ray Findings: Degree of Cardiac Enlargement (*per Centum*)	Electrocardiographic Findings: Pattern of *QRS* Complex in Lead V_1
1	35	M.	+	–	–	–	–	–	–	–	–	–	S.R.[5]	+	+	+		–	N	N	N	U–U	–	N	–	+5	*rS*
2	37	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	+	+		–	N	+	N	U–U	–	N	–	+8	*rS*
3	29	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	+	+		–	N	+	N	UU	–	N	–		*rS*
4	25	F.	+	–	+	–	+	–	–	–	–	–	S.R.	+	+	+		–	N	+	+	U–U	–	N	–	+12	*rS*
5	26	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	–	+		+	N	+	N		–	N	–	+7	*rS*
6	37	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	+	+	+	–	N	N	N	))	–	N	–	0	*rS*
7	40	F.	+	+	+	–	–	–	–	–	–	–	S.R.	+	(Ex)[6]	+	+	1	N	+	N	U–U	–	N	–	+10	*RSR*
8	23	M.	–	+	–	–	–	–	–	–	–	–	S.R.	+	+	+		+	T	+	N	U–U	–	N	–	+22	*rS*
9	39	F.	–	–	–	–	–	–	+	–	–	–	S.R.	+	–	+		2	N	+	N		–	N	–	0	*RSR*
10	41	F.	–	–	–	–	–	–	+	–	–	–	S.R.	+	–	+		–	N	+	N	U–U	–	N	–	0	*rS*
11	22	F.	–	–	–	+	–	–	–	–	–	–	S.R.	+	+	+		3	N	+	N	U–U	–	N	–	+5	*RSR*
12	20	F.	+	+	–	+	+	–	–	–	–	–	S.R.	+	+	+		–	N	+	N	UU	–	N	–	+5	*rS*
13	39	F.	–	–	–	+	–	–	–	–	–	–	S.R.	+	+	+		–	N	N	N	))	–	N	–	+25	*rS*
14	27	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	–	+	+	–	N	+	N		–	N	–	0	*RS*

[1] Numerals indicate intensity of murmur; + = murmur present, intensity not recorded.
[2] N, normal; T, "tapping".
[3] I and U = aortic and pulmonary compounds of sound; + = accentuation;)) = no splitting; UU = grade I splitting; U–U = grade II splitting.
[4] S = small.
[5] S.R., sinus rhythm; A.F., auricular fibrillation.
[6] Felt after exercise only.

TABLE I.—*Continued*

Case Number	Age (Years)	Sex	Symptoms: Pulmonary Hypertension: Frank Hæmoptysis	Acute Episodic Dyspnœa after Effort	Nocturnal Paroxysmal Dyspnœa	Recurrent "Bronchitis"	"Pneumonia and Pleurisy"	Central Chest Pain	Low Cardiac Output: Excessive Fatigue	Low Cardiac Output: Effort Syncope	Congestive Cardiac Failure: Ankle Œdema	Congestive Cardiac Failure: Frank Failure	Clinical Signs: Rhythm	Diagnostic Signs of Mitral Stenosis: Apical Diastolic Murmur	Apical Diastolic Thrill	Accentuated Apical First Heart Sound	Opening Snap	Apical Systolic Murmur[1]	Pulmonary Hypertension: Character of Apex Beat[2]	Right Ventricular Pulsation	Pulmonary Artery Pulsation	Pulmonary Second Sound[3]	Graham Steell Murmur	Low Cardiac Output: Volume of Radial Pulse[4]	Coldness and Cyanosis of Extremities	X-Ray Findings: Degree of Cardiac Enlargement (*per Centum*)	Electrocardiographic Findings: Pattern of *QRS* Complex in Lead V_1
Class III																											
15	42	M.	+	–	–	–	–	–	–	–	–	–	A.F.[5]	+	–	+	+	–	T	+	N	U–U+	–		+	+25	*rSr*
16	36	M.	+	–	–	–	–	–	–	–	–	–	S.R.	+	–	+	+	–	T	+	N	U–U+	–	N	–	+25	*rS*
17	27	F.	–	–	+	–	–	–	–	–	–	–	S.R.	+	+	+		–	T	+	N	UU	–	N	–	+7	*RS*
18	39	F.	–	–	+	–	–	–	+	+	+	–	A.F.	+	+	+		2	T	+	N	U–U+	–	S	+	+24	*RSR*
19	37	F.	–	–	–	+	–	–	+	–	–	–	S.R.	+	+	+		1	T	+	+	UU+	–	N	–	+26	*rS*
20	38	F.	–	–	–	–	–	–	+	–	–	–	S.R.	+	+	+		2	T	+	+	U–U+	–	N		+34	*RSR*
21	25	F.	+	–	–	–	–	–	–	–	–	–	S.R.	+	–	+	+	–	T	+	N	U–U	–	N	–	+20	*RSR*
22	33	F.	–	+	+	+	+	–	–	–	–	–	S.R.	+	+	+		–	T	+	+	UU+	–	N	–	+39	*RSR*
23	35	F.	–	+	+	–	–	–	+	–	+	–	S.R.	+	–	+		2	T	+	+	U–U	–	N	–	+19	*RS*
24	47	F.	–	+	–	–	–	–	–	–	–	–	S.R.	+	+	+		–	T	+		UU	–	N	–	+25	*RS*
25	32	F.	+	–	–	+	–	–	–	–	–	–	S.R.	+	–	+		–	T	+	N	U–U+	–	N	–	+10	*RSR*
26	37	F.	–	–	–	–	–	+	+	–	–	–	A.F.	+	–	+	+	1	T	+	N	U–U+	–	N	–	+15	*rS*
27	36	F.	+	–	–	+	+	–	–	–	–	–	S.R.	+	–	+	+	2	T	+	N	U–U+	–	N	–	+42	*RSR*
28	28	M.	+	+	–	–	–	–	–	–	–	–	A.F.	+	+	+	–	–	T	+	N	U–U+	–	N	–	+42	*RSR*
29	19	F.	+	+	–	–	+	–	+	–	+	–	S.R.	+	+	+	+	–	T	+	N	U–U+	+	S	+	+26	*QR*
30	19	M.	–	–	–	–	–	–	+	–	–	–	A.F.	+	–	+		–	T	+	N		–	S	–		
31	38	F.	–	–	–	–	–	–	+	–	–	–	A.F.	+	+	+		–	T	+	N	UU+	–	S	+	+18	*RSR*
32	42	M.	–	+	–	–	–	–	+	–	–	–	S.R.	+	–	+		1	N	+	N	U–U	–	S	+	+43	*QR*
33	39	M.	+	+	+	–	–	–	–	–	–	–	A.F.	+	+	+	+	–	T	+	+	UU+	–	S	–	+37	*RSR*
34	25	F.	–	–	–	–	–	–	–	–	–	–	S.R.	+	+	+	+	–	T	+	N	U–U	–	S	–	+20	*RS*
35	36	F.	–	+	–	–	–	–	–	–	+	–	S.R.	+	+	+	+	–	T	+	N	U–U	–	N	+	0	*RSR*
36	43	M.	+	–	–	–	–	–	–	–	+	–	S.R.	+	–	+		–	T	+	+	UU+	–	S		+37	*QR*

36	43	M.	+	−	−	−	−	−	−	−	+	−	S.R.	+	−	+		−	T	+	+	U^{+}U	−	S		+37	*QR*
37	24	M.	−	−	−	−	−	−	−	+	−	−	S.R.	+	−	+		−	T	+	+	U^{+}U	−	S	−	+28	*QR*
38	33	F.	−	+	−	−	−	−	+	−	−	−	S.R.	+	+	+		−	T	+	+	U-U^{+}	−	N	+	+41	*RSR*
39	42	F.	−	−	−	−	−	−	+	−	−	−	S.R.	+	+	+		−	T	+	N	U-U^{+}	−	S	−	+19	*RSR*
40	47	M.	+	−	+	−	−	−	+	−	+	−	A.F.	+	+	+		2	T	+	N	U-U^{+}	−	S	+	+34	*RSR*

Class IV

41	37	F.	+	+	−	−	+	−	−	−	+	−	S.R.	+	+	+		−	T	+	N	U-U^{+}	−	N	−	+20	*RS*
42	23	M.	+	+	−	−	−	−	−	+	+	+	S.R.	+	−	+		1	T	+	+	U^{++}U	+	S	+	+34	*R*
43	23	F.	+	−	+	+	+	−	+	−	+	−	S.R.	+	+(Ex)[6]	+	+	2	T	+	+	U^{++}U	+	S	−	+20	*QR*
44	45	F.	−	−	−	−	−	−	+	−	+	−	S.R.	+	+	+	+	2	T	+	N	U-U^{+}	−	S	+	+32	*QR*
45	23	F.	−	−	−	−	+	−	+	−	+	−	A.F.	+	+		−	3	T	+	+	U-U^{+}	−	S	+	+50	*QR*
46	39	F.	−	+	+	−	−	+	−	−	+	−	S.R.	+	+	+	+	1	T	+	N	U^{++}U	−	N	+	+25	*QR*
47	27	F.	−	−	−	+	−	+	+	−	+	−	S.R.	+	+	+	+	1	T	+	+	U-U	−	S	−	+39	*RSR*
48	30	M.	−	−	−	−	+	−	−	−	+	+	A.F.	+	+	+		−	T	+	+	U^{++}U	−	S	+	+50	*QR*
49	24	F.	+	−	−	+	−	−	+	−	−	−	S.R.	+	+	+		2	T	+	N	U-U^{+}	−	S	−	+33	*RSR*
50	46	F.	−	−	−	−	+	−	−	−	+	+	A.F.	+	−	+		+	T	+	N	U-U^{+}	−	S	+	+45	*QR*
51	54	F.	−	−	−	−	+	−	+	−	+	−	A.F.	+	+	+		2	T	+	+	U-U^{+}	−	S	+	+30	*RSR*
52	32	F.	+	+	−	+	+	−	−	−	+	−	S.R.	+	+	+		+	T	+	N	U^{+}U	+	N	−		*RSR*
53	22	F.	−	−	−	−	−	−	−	−	+	−	S.R.	+	+	+		+	T	+	N	U^{++}U	−	S	−	+46	*QR*
54	39	F.	+	−	−	−	−	−	−	−	+	−	S.R.	+	−	+		−	T	+	N	U-U^{+}	+	N	+	+32	*RSR*
55	34	M.	+	+	−	−	−	−	+	−	+	+	A.F.	+	−	+		−	T	+	+	U^{++}U	+	S	+	+37	*QR*
56	43	F.	−	−	−	−	+	−	−	−	+	−	S.R.	+	+	+		−	T	+	+	U^{+}U	−	S	+		*QR*
57	30	F.	−	+	−	−	+	−	−	−	+	−	S.R.	+	+	+		−	T	+	N	U-U^{+}	+	N		+50	*R*

[1] Numerals indicate intensity of murmur; + = murmur present, intensity not recorded.
[2] N, normal; T, "tapping".
[3] U and U=aortic and pulmonary compounds of sound; + = accentuation; ⌣=no splitting; UU=grade I splitting; U-U=grade II splitting.
[4] S=small.
[5] S.R., sinus rhythm; A.F., auricular fibrillation.
[6] Felt after exercise only.

First Heart Sound and Opening Snap.—An accentuated first heart sound was invariably present. An opening snap was noted in 16 patients (three in Class II, nine in Class III and four in Class IV). It was best heard either in the third left intercostal space three to five centimetres lateral to the parasternal line, or immediately to the left of the sternum in the third and fourth intercostal spaces. It was also usually audible at the mitral area.

Sellors, Bedford and Somerville (1953) believe that stenosis is likely to be the predominant lesion in the presence of a snapping first sound ("closing snap" of the valve), a loud opening snap and a "tapping" apex beat. They also found that this triad frequently indicated the diaphragmatic type of stenosis most amenable to surgery. Brigden and Leatham (1953) mentioned the frequency with which an opening snap was heard in stenotic lesions, in contrast to its absence in pure mitral incompetence. Similarly they found that the first sound was characteristically accentuated in stenosis, but was normal with an incompetent valve. Mounsey (1953) discussed the differentiation of the opening snap from the delayed pulmonary element of the split second heart sound. In the present series, the invariable finding of accentuation of the first heart sound confirms the experience of these authors. An opening snap was recorded with considerably less frequency.

Apical Systolic Murmur.—A systolic murmur was audible at the apex in 25 of the 57 patients, being most frequent in Class IV. The intensity of the murmur was classified as grade I in seven cases, grade II in 10 cases and grade III in two cases. In the remaining six the intensity was not recorded. At operation only two patients (Cases 40 and 42) had significant mitral regurgitation in addition to stenosis, and both had grade I systolic murmurs before operation.

The frequency with which a systolic murmur is heard in a purely or predominantly stenotic lesion is well illustrated by its occurrence in almost half the cases. In the great majority, the murmur was only of grade I or grade II intensity; but amongst those with a very soft murmur were the two patients in whom significant regurgitation was found at operation. By contrast, the two patients with grade III systolic murmurs had purely stenotic lesions. Recording similar experience, Gorlin *et alii* (1952) found that 40% of patients with pure stenosis had apical systolic murmurs of grade II intensity or greater. Moreover, five of their patients, proved to have significant regurgitation at the time of valvotomy, had no apical systolic murmur. Venner and Holling (1953) found that a loud murmur (grade IV), and even a thrill, was not a certain indication that the valve is unsuitable for valvotomy—that is, that the lesion is predominantly regurgitant. In their experience the character of the murmur was of little diagnostic assistance.

SYMPTOMS AND SIGNS OF PULMONARY HYPERTENSION

Symptoms

Under the heading of symptoms of pulmonary hypertension were included hæmoptysis, chronic exertional dyspnœa, the more acute episodic types of dyspnœa and central chest pain associated with effort.

Hæmoptysis.—Frank hæmoptysis, as distinct from streaking of the sputum with blood, had occurred in 21 of the 57 cases (four in Class II, 10 in Class III and seven in Class IV), and except for dyspnœa on exertion was the commonest single symptom. In five patients it was the first symptom of their heart disease. Fourteen of the 21 had experienced other acute pulmonary symptoms in addition to hæmoptysis.

The mitral valve area was definitely reduced in all but one case (Case 1) with hæmoptysis, being 1·0 square centimetre or less in 14 patients and 1·5 square centimetres or less in the remaining six. Most of the patients had only moderate elevation of the pulmonary arteriolar resistance (Figure I).

These findings are similar to those of Lewis *et alii* (1952). These authors postulate that when there is a low pulmonary arteriolar resistance, a sudden rise in right ventricular output causes a rapid increase in pressure in the pulmonary capillaries and small veins. This rise in pressure is transmitted to the broncho-pulmonary varices, if these are present, and may result in rupture and consequent hæmoptysis, as suggested by Ferguson *et alii* (1944). Absence of broncho-pulmonary varices would have to be invoked to explain the lack of hæmoptysis in other patients with similar physiological findings.

Dyspnœa.—All patients complained of breathlessness on exertion, and in 40 it was the first symptom. Its severity increased progressively through the three functional classes. In addition, acute episodic types of dyspnœa were common and were broadly classified into two groups, as follows: group I, acute respiratory illnesses characterized by fever and dyspnœa; group II, acute pulmonary congestion sometimes progressing to pulmonary œdema.

The milder episodes in group I were usually described by the patient as " bronchitis ". When more severe they had frequently been diagnosed as " pneumonia " or " pleurisy and pneumonia ", often accompanied by localized chest pain and hæmoptysis. Some undoubtedly represented episodes of pulmonary infarction. Illnesses of this type occurred in 20 cases (four in Class II, five in Class III, and 11 in Class IV). The milder episodes were equally frequent in the three functional classes. Pneumonia or

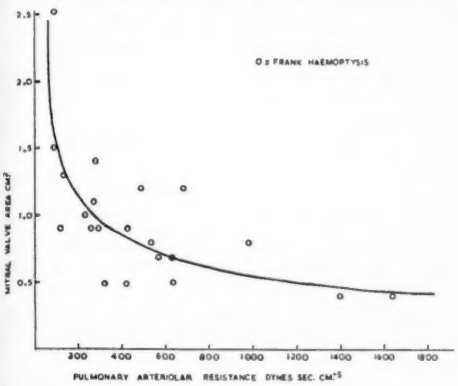

FIGURE I

The majority of patients with a history of frank hæmoptysis had only mild or moderate elevation of the pulmonary arteriolar resistance. The curve represents the relationship between mitral valve area and pulmonary arteriolar resistance for the whole series

" pneumonia and pleurisy " were more common in Class IV, and occurred in nine of the 17 cases in this class. Both the mild and the more severe grades of illness included in this group probably had a varied pathological basis, including acute respiratory infections, attacks of pulmonary congestion with little infection and episodes of pulmonary infarction with pleuritic pain and hæmoptysis. There were no distinguishing physiological findings in this group.

In group II, the attacks either (*a*) were associated with unusual exertion, emotional stress or pregnancy, or (*b*) occurred at night at rest as attacks of acute nocturnal paroxysmal dyspnœa.

(*a*) Sixteen patients complained spontaneously of one or more attacks of acute dyspnœa associated with effort and in an additional three (Cases 22, 29 and 32) pulmonary œdema occurred on exercise during cardiac catheterization. Four of these 19 patients were in Class II, nine in Class III, and six in Class IV. The pulmonary capillary pressure on exercise was measured in 10 cases; it was found to exceed 35 millimetres of mercury in eight cases and was 28 and 30 millimetres in the remaining two (Figure II). In a further eight cases only the resting pressure was obtained. In six of these it was greater than 25 millimetres of mercury. There were four other patients in the series (Cases 25, 34, 46 and 50) with pulmonary capillary pressures exceeding 35 millimetres on exercise who did not have a history of acute episodes of dyspnœa associated with effort. However, three of them (Cases 25, 46 and 50) had experienced either nocturnal paroxysmal dyspnœa or " recurrent respiratory infections ".

(*b*) Acute nocturnal paroxysmal dyspnœa had occurred in 11 cases (two in Class II, seven in Class III and two in Class IV). All had a resting pulmonary capillary pressure of less than 30 millimetres of mercury. Otherwise the physiological findings were similar to those found in the patients with acute episodes of dyspnœa associated with effort.

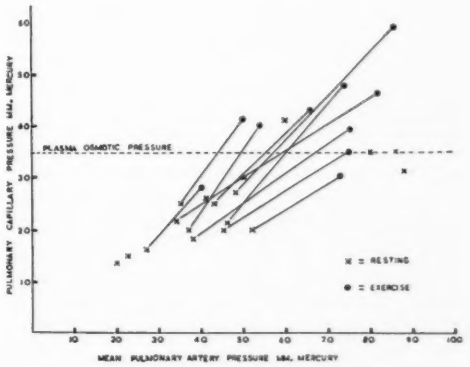

FIGURE II

In patients with a history of episodes of acute dyspnœa or pulmonary œdema following effort, the pulmonary capillary pressure during exercise usually exceeded the plasma osmotic pressure (approximately 35 millimetres of mercury). Sometimes it approached or exceeded this level even at rest

Gorlin *et alii* (1951) emphasized the critical role of the pulmonary capillary pressure in the production of pulmonary œdema, and pointed out the frequency with which œdema occurs when the pressure exceeds the normal plasma osmotic pressure of 35 millimetres of mercury. Further, their findings, and those in the present series, show that when the pulmonary capillary pressure approaches this " transudation level " at rest, the pulmonary arteriolar resistance increases rapidly, apparently as a " protective "

measure. It seems likely that in these patients who had experienced episodes of acute pulmonary congestion and œdema, the pulmonary arteriolar resistance at least on exercise was not great enough to "protect" the pulmonary capillaries (Figure III). The tachycardia accompanying exercise, by shortening diastole during which mitral valve flow occurs, contributes further to the pulmonary congestion and the rise in pulmonary capillary pressure.

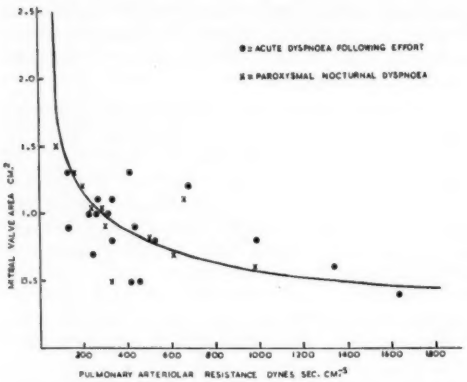

FIGURE III

The incidence of acute dyspnœa or pulmonary œdema following effort and of paroxysmal nocturnal dyspnœa was greatest among those patients with only moderate elevation of the pulmonary arteriolar resistance

In acute nocturnal dyspnœa also the basic factors of pulmonary congestion and transudation into the alveoli are probably operative. Recumbency and possibly the increased blood volume associated with sleep (Perera and Berliner, 1943) may act as precipitating factors; but the exact mechanism of this symptom remains uncertain.

Central Chest Pain on Effort.—Inframammary aching or discomfort was a common symptom. Sometimes it was related to effort; but in character, site and duration it differed from the pain of myocardial ischæmia. On the other hand, central or substernal chest pain on effort was uncommon, and was met with in only three patients (Cases 26, 46 and 47), aged thirty-seven, thirty-nine and twenty-seven years respectively. The physiological and radiological findings in these three cases did not present any distinctive features. Right ventricular hypertrophy was evident in the electrocardiogram of the two patients in Class IV and was absent in the one patient in Class III. The *T* wave was inverted in leads V_1 and V_2 in Case 46, but this was regarded as part of the pattern of right ventricular hypertrophy. No tracings were obtained in these cases after effort or while the pain was present.

Burgess and Ellis (1942), reviewing the subject of chest pain in mitral stenosis, named four varieties: the pain associated with cardiac neurosis; that of active rheumatic carditis; *angina pectoris*; and "hypercyanotic angina" (Vaquez and Giroux, 1908). Viar and Harrison (1952) describe paroxysmal chest pain in six patients with pulmonary hypertension of varied ætiology including mitral stenosis. They suggest that the most likely cause of the pain is distension of the main pulmonary artery secondary to the pulmonary hypertension.

In the three patients in the present series, no evidence of coronary disease was observed at operation, and it is possible that their effort pain was of this "pulmonary hypertensive" type.

Clinical Signs

The degree of pulmonary hypertension was judged by the character of the apex beat, the degree of pulsation over the right ventricle, the character of the pulmonary second sound, the palpability of pulsation over the pulmonary artery and the presence or otherwise of a Graham Steell murmur.

The Apex Beat.—The apical impulse in mitral stenosis was described as "tapping" in quality by Sansom (1892). Right ventricular hypertrophy and a palpable loud first heart sound combine to produce this tapping sensation (Abrahams and Wood, 1951).

The apex beat was recorded as normal in all patients in Class II, except Case 8, and right ventricular or "tapping" in all patients in Classes III and IV, except Case 32 in Class III.

With one exception (Case 32) a normal apex beat was associated with a resting pulmonary arterial pressure of 30 millimetres of mercury or less. Conversely (except for Cases 15, 19 and 40), all patients with a right ventricular apical impulse had a pulmonary arterial pressure above 30 millimetres of mercury. On the basis of these findings a right ventricular apex beat means at least moderate pulmonary hypertension.

Electrocardiographically, right ventricular hypertrophy was absent in all patients with a normal apex beat, and radiologically only two (Cases 3 and 25) had significant cardiac enlargement. One of these (Case 28) had auricular fibrillation.

Right Ventricular Pulsation. The increased systolic thrust of a hypertrophied right ventricle is transmitted through the chest wall as a visible and palpable heave between the apex beat and the left sternal border.

In Table I the pulsation between the apex beat and the sternum is recorded for each patient as normal or increased. In four cases it was considered normal (Cases 1, 6, 10 and 13 in Class II). The mean resting pulmonary arterial pressure in these cases was respectively 10, 15, 25 and 27 millimetres of mercury—that is, in none did it exceed 30 millimetres of mercury at rest. All patients were in sinus rhythm. Electrocardiographically none showed evidence of right ventricular hypertrophy (all had *rS* pattern in lead V_1). The heart size was normal in three (Cases 1, 6 and 10) and moderately enlarged in one (Case 13).

Of the 53 patients who had increased pulsation over the right ventricle, only nine had a mean resting pulmonary arterial pressure of less than 30 millimetres of mercury (Cases 3, 4, 7, 15, 19, 28, 30, 31 and 40). One patient (Case 3) was three months pregnant, and the finding of a slightly increased pulsation may have been due to this. Of the remaining eight, it seems significant that five (Cases 15, 19, 28, 31 and 40) had auricular fibrillation, and four of these had significant cardiac enlargement. All five had some evidence of right ventricular hypertrophy in the electrocardiogram (*RSr* pattern in lead V_1). One of the three in sinus rhythm (Case 19) had moderate cardiac enlargement. It seems, therefore, that with very few exceptions, increased right ventricular pulsation indicates a mean pulmonary arterial pressure of at least 30 millimetres of mercury unless the patient has auricular fibrillation. In the latter case, the clinical signs of right ventricular enlargement together with supporting radiological and electrocardiographic evidence tend to be accompanied by a lower pulmonary arterial pressure than would be expected in the presence of sinus rhythm. Such a relationship for all the patients in Class III has already been pointed out in the second paper of this series.

The Pulmonary Second Sound.—In mitral stenosis, the second heart sound in the pulmonary area is frequently abnormal, either in the degree of separation of aortic and pulmonary elements—so-called "splitting"—or in the increased intensity of the pulmonary element, or in both. All combinations of splitting and accentuation were found in the 50 cases in which the character of the second heart sound was recorded (Table I).

Only six patients had a normal sound (Cases 3, 6, 12, 24 and 27), and in these the resting pulmonary arterial pressure was less than 40 millimetres of mercury. Apart from these six patients, mild pulmonary hypertension was not associated with a constant type of second sound, except that the intensity of the pulmonary element was never more than slightly increased. With moderately severe pulmonary hypertension, grade II splitting was frequent, especially if the ventricular complex in lead V_1 had an *RSR* pattern. Some accentuation of the pulmonary element was not uncommon. In severe pulmonary hypertension the sound was often closely split; sometimes grade II splitting was perceptible. Accentuation of the pulmonary component was usually marked, giving the sound a ringing quality.

The rationale of these changes is not completely understood. Increased intensity of the second sound is a logical consequence of pulmonary arterial hypertension; but the relative timing of the two components is more difficult to explain. Either delayed excitation of the right ventricle, due to its increased muscle mass, or prolongation of right ventricular systolic ejection time would delay closure of the pulmonary valve and cause separation of the aortic and pulmonary elements. In either case the splitting might be expected to increase progressively with increasing severity of the pulmonary hypertension. However, it has been shown that severe pulmonary hypertension is quite often accompanied by barely perceptible splitting—at least to the human ear. Leatham (personal communication), from phonocardiographic studies, believes "but without full evidence" that the proximity of the two elements under these circumstances is an auscultatory illusion, as the ear has difficulty in perceiving a soft sound (the aortic element) immediately followed by a loud sound (the accentuated pulmonary element). He considers that there is no great change in the timing of the pulmonary second sound in pulmonary hypertension unless there is electrical delay of activation of the right ventricle as shown in the electrocardiogram.

Pulmonary Artery Pulsation.—In patients with a thin chest wall, enlargement of the pulmonary artery is detectable as a palpable and sometimes visible pulsation in the second left intercostal space. This sign was noted in 17 cases in the present series. One patient (Case 4) in Class II had only first degree enlargement of the pulmonary artery on radiological examination. Eight patients (Cases 19, 20, 22, 23, 33, 36, 37 and 38) were in Class III, and seven of these had grade II pulmonary artery enlargement, while one (Case 57) had grade III enlargement. The highest incidence was in Class IV, in which the sign was recorded as present in nine of the 17 patients (Cases 42, 43, 45, 47, 48, 41, 55 and

56). Radiologically, three of the eight had "++" enlargement of the pulmonary artery, four had "+++" enlargement and one had "++++" enlargement. The resting pulmonary arterial pressure was less than 30 millimetres of mercury in only two and above 50 millimetres of mercury in nine of the 17 cases. It may be concluded that the presence of this sign usually denotes at least moderate, and often severe, pulmonary hypertension, and grade II, or greater, enlargement of the pulmonary artery.

Graham Steell Murmur.—A basal diastolic murmur considered to be of the Graham Steell type, due to pulmonary valvular incompetence, was heard in seven cases (Cases 29, 42, 43, 52, 54, 55 and 57). All the patients had severe pulmonary hypertension, significant cardiac enlargement and "+++" or greater enlargement of the pulmonary artery (except for "++" enlargement in Case 29).

Relationship between Clinical Signs and Pulmonary Artery Pressure.—In the mildest cases (mean pulmonary artery pressure less than 30 millimetres of mercury) the apex beat was of normal character. There was slight, if any, increase in the systolic thrust over the right ventricle. Pulsation of the pulmonary artery was rarely palpable. The second heart sound in the pulmonary area was normal or showed some splitting, with usually no, or minimal, accentuation of the pulmonary element.

With moderately severe pulmonary hypertension (pulmonary arterial pressure from 30 to 45 millimetres of mercury) the apex beat had become "tapping" (or right ventricular) in character. There was an increased systolic heave over the right ventricle. The pulmonary second sound was frequently split, particularly if lead V_1 in the electrocardiogram showed an *RSR* complex. There was commonly some accentuation of the pulmonary element of the sound.

In the severe or extreme cases (pulmonary artery pressure from 45 to 85 millimetres at rest), the apical impulse was tapping, and there was an unmistakable systolic heave over the right ventricle. In the second left intercostal space, pulsation over the pulmonary artery was felt and was accompanied by a palpable shock synchronous with the second heart sound. The second heart sound was sometimes perceptibly split, but commonly splitting was appreciated with difficulty because of the greatly accentuated pulmonary element of the sound. A Graham Steell murmur was frequently present.

SYMPTOMS AND SIGNS OF REDUCED CARDIAC OUTPUT

Symptoms

Twenty patients complained of excessive fatigue. Gorlin *et alii* (1952) found that fatigue was a more prominent feature of combined mitral regurgitation and stenosis than of pure stenosis. They consider that the symptom results from the combined effect of the two lesions in restricting aortic output and systemic blood flow. In the present series, in which stenosis was the dominant lesion, dyspnœa of effort was more incapacitating than fatigue.

Syncopal Attacks on Effort.—As a symptom of mitral stenosis, fainting on exertion has received little attention in the literature, probably because of its infrequency. Actual loss of consciousness was found in only three cases in the present series (Cases 18, 37 and 42). The first two patients were in Class III and the third in Class IV. All had a much reduced valve area (1·1, 0·7 and 0·2 square centimetres respectively) and a low cardiac index, with little or no increase in cardiac output on exercise. The stroke index was low at rest, and in Cases 18 and 37 it fell still further on exercise. The mean pulmonary arterial pressures were respectively 44, 57 and 88 millimetres of mercury at rest, and 82, 105 and 92 millimetres on exercise.

The most striking history was given by the second patient (Case 37), a young man, aged twenty-four years, in sinus rhythm, whose chief complaint was one of syncopal attacks on effort. It is perhaps significant that he had a greater degree of pulmonary hypertension than any other patient in the same functional class.

Howarth and Lowe (1953) investigated effort syncope in two cases of primary pulmonary hypertension, and found that the faint was preceded by a gradual fall in systemic blood pressure. At the same time there was a decrease in the systolic pressure and an increase in the end diastolic pressure in the right ventricle. These findings suggested acute right ventricular failure, presumably precipitated by the increase of pulmonary hypertension which occurs with exercise. The gradual fall in systemic blood pressure was in contrast to the sudden hypotension characteristic of vaso-vagal syncope, in which muscular vasodilatation leads to a rapid fall in peripheral resistance (Barcroft *et alii*, 1944). In mitral stenosis, as in primary pulmonary hypertension, effort syncope could well be due to acute right ventricular failure. A rise in filling pressure in the right side of the heart is frequently observed in the more severe cases in response to exercise. No observations

have been made during a syncopal attack in any of these cases.

Clinical Signs

An abnormally low output and poor peripheral flow were reflected in a small pulse volume and coldness and cyanosis of the extremities. The pulse volume was recorded as normal in all patients in Class II. None of these patients had undue coldness of the extremities or peripheral cyanosis. In Class III, 11 of the 22 patients had a diminished pulse volume and eight had coldness and or cyanosis of the extremities. In the severely affected patients of Class IV, only five of the 17 had a pulse of normal volume, and they were all in sinus rhythm. Eight of the 12 with a small pulse had also cold and or cyanosed extremities.

Arterial Oxygen Saturation and Cyanosis.—A lowered arterial oxygen saturation was found to be present at rest in eight of 16 patients in Group IV. Six of the eight (Cases 42, 44, 45, 50, 51 and 55) were noted clinically as having cyanosis, but this was more evident in the extremities than in the lips and mucous membranes. Moreover, all had cold hands and a small pulse volume.

When the arterial oxygen saturation is significantly below normal, cyanosis must be partly of the central type (Lundsgaard and Van Slyke, 1923); but the clinical and physiological evidence suggests that the peripheral factor is the more important.

THE COMPLICATIONS OF MITRAL STENOSIS

Auricular Fibrillation. — Physiological evidence of the detrimental effect of auricular fibrillation has been referred to in the first paper of this series. It was shown that this arrhythmia occurs with increasing frequency as the mitral valve area falls below 1·5 square centimetres. The earlier it occurs in the course of the disease, the more obvious is the associated fall in cardiac output. In the later stages (Group IV), the systemic blood flow is low in all patients and is not further reduced in the presence of auricular fibrillation.

The effect of this arrhythmia on heart size was discussed in the second paper. In all functional classes, auricular fibrillation was associated with a greater degree of cardiac enlargement. Electrocardiographically, 12 of the 13 patients had evidence of right ventricular hypertrophy.

Clinically, right ventricular enlargement was generally greater than might have been expected from the degree of pulmonary hypertension. Peripheral signs of diminished cardiac output were more frequently present than in patients with sinus rhythm.

Congestive Cardiac Failure.—The patients in this series do not represent a complete cross-section of the clinical picture of mitral stenosis, and examples of the more advanced stages of chronic congestive cardiac failure are lacking. Only one patient (Case 55) had congestive failure at the time of study. An additional three (Cases 42, 48 and 50) subsequently developed this complication. Œdema of the ankles had been noticed intermittently by 16 of the 17 patients in Class IV, and many had at some time been treated with digitalis and mercurial diuretics. In some instances the peripheral œdema was probably due to congestive cardiac failure; but as it did not recur during the period of observation these patients are not included in the "failure" group.

Of the four patients classified as having congestive cardiac failure, three (Cases 48, 50 and 55) were in auricular fibrillation, and one (Case 42) was in sinus rhythm. None of the three patients with auricular fibrillation had recently had symptoms of acute pulmonary congestion or œdema. All three had severe pulmonary hypertension and a raised mean right auricular pressure at rest. The mitral valve area was 0·5 square centimetre or less. The cardiac index was respectively 1·4, 1·7 and 1·3 litres per square metre per minute. The patient in sinus rhythm had equally severe pulmonary hypertension. The right auricular mean pressure at rest was at the upper limit of normal. The mitral valve area was 0·8 square centimetre and the cardiac index 2·6 litres per square metre per minute. This patient had recently had hæmoptysis and episodes of pulmonary œdema.

Lewis *et alii* (1952) found that patients with both œdema and hepatomegaly formed a distinct physiological and clinical group. They "represented the opposite pole from those patients with frequent hæmoptyses. Paroxysmal respiratory symptoms had been displaced by signs of peripheral failure as the leading feature in their illness." Sellors *et alii* (1953) also contrasted patients incapacitated by pulmonary œdema with those in advanced congestive cardiac failure with auricular fibrillation, in whom acute episodes of dyspnœa were no longer prominent.

Despite their short history of decompensation, three of the four patients in the present group conformed with the description of congestive cardiac failure given by the above-mentioned authors. The one patient in sinus rhythm was apparently in an earlier transitional stage, in

which acute pulmonary congestion and early cardiac failure were present at the same time.

Peripheral Embolism.—In this series, systemic arterial embolism was a very uncommon complication. One patient (Case 34), in sinus rhythm at the time of examination, had had a sudden hemiplegia, following a confinement two and a half years previously. Another (Case 3) gave a doubtful history of a similar episode.

Subacute Bacterial Endocarditis.—As far as could be ascertained, no patient had had subacute bacterial endocarditis. Brigden and Leatham (1953) have emphasized its relative rarity in pure mitral stenosis in contrast to its high incidence (10 of their 30 cases) in pure mitral incompetence.

SUMMARY

In a series of three papers, the clinical, physiological, radiological and electrocardiographic findings in 57 cases of mitral stenosis have been described and correlated. All the patients had been referred to us for assessment as to their suitability for valvotomy, and 48 were subsequently submitted to operation.

All patients had symptoms due to their cardiac lesion. Increasing disability was found to be associated with diminishing mitral valve area, increasing hypertension in the pulmonary vascular tree and a progressive reduction of cardiac output, both at rest and on exercise. Functional impairment was mild with valve areas greater than 1·5 square centimetres and severe if the valve area was less than 1·0 square centimetre.

The average age for the whole series was thirty-three years, and there was no correlation between chronological age and the severity of the disease. Similarly, severity was not determined by the intensity of the preceding acute rheumatic history.

The clinical signs of a stenotic mitral valve have been discussed in some detail. A definite opening snap preceding the classical mid-diastolic murmur together with an accentuated first heart sound were found to indicate a predominantly stenotic lesion. These findings are in agreement with those of previous authors.

An apical systolic murmur was heard in almost half the patients but, with two exceptions, did not indicate the presence of mitral regurgitation as determined at operation.

The clinical evidence of pulmonary hypertension reflected closely the pulmonary arterial and capillary pressures found on cardiac catheterization. Hæmoptysis, acute and chronic forms of dyspnœa and central chest pain on effort have been considered as symptoms of the increased pulmonary vascular pressures, and their mechanism has been discussed. The clinical signs of pulmonary hypertension were found to be minimal or absent when the mean pulmonary arterial pressure was less than 30 millimetres of mercury at rest. These findings applied to patients in functional Class II. Moderately severe (30 to 50 millimetres of mercury) and severe (more than 50 millimetres of mercury) degrees of pulmonary hypertension were found in Classes III and IV respectively. Radiologically evident cardiac enlargement, and evidence of right ventricular hypertrophy in the electrocardiogram increased progressively through the functional classes. The only exceptions to this rule were the patients with auricular fibrillation, in some of whom the pulmonary arterial pressure was found to be lower than the clinical, radiological and electrocardiographic findings suggested.

The reduced cardiac output was evidenced by diminished pulse volume and cold extremities. Syncopal attacks on effort were not common, but in one case were a striking symptom.

Thirteen of the 57 patients had auricular fibrillation. The unfavourable effect of this complication was demonstrated in the clinical, radiological and physiological findings.

Four patients had congestive cardiac failure. All had severe pulmonary hypertension and a very low cardiac output at rest, with no significant increase on exercise. No patient in this group had a mitral valve area greater than 0·8 square centimetre.

Peripheral arterial embolism was an uncommon finding. Subacute bacterial endocarditis was not encountered.

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INTRACRANIAL ARTERIAL ANEURYSMS[1]

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In this communication it is intended to describe the frequency, site and other characteristics of cerebral aneurysms and to emphasize the lack of contrast between the age incidence of hæmorrhage from ruptured aneurysms on the one hand and cerebral hæmorrhage in general on the other.

Material

The material in the present series consists of 182 cases of aneurysm proven at autopsy. They were collected from the post-mortem records of the Royal Prince Alfred Hospital from 1912 to 1953, and of Sydney Hospital from 1919 to 1953. The remaining few were from Saint Vincent's Hospital, the Royal North Shore Hospital of Sydney and the Sydney City Morgue.

In order to compare the age incidence of ruptured aneurysm with that of cerebral hæmorrhage proper, 353 cases of the latter disease were collected from the post-mortem records of the Royal Prince Alfred Hospital from 1910 to 1953. Only cases in which the autopsy findings indicated them to be undoubtedly spontaneous and not secondary to aneurysm, blood dyscrasias, tumours or trauma were included. No case of so-called idiopathic ventricular or subarachnoid hæmorrhage was included.

Frequency

Intracranial aneurysms, sometimes called "berry aneurysms", are stated to account for about 0·5% to 1·5% of autopsy material (Richardson and Hyland, 1941), but as Schmidt (1930) stressed, the closer the post-mortem examination of the cerebral arteries, the more frequently will aneurysms, symptomless during life, be found.

Sometimes the aneurysm, if associated with subarachnoid hæmorrhage, is not found at autopsy, the hæmorrhage then being attributed to rupture of a vessel, as the result of atheroma or hypertension.

In all the 800 autopsies conducted at the Royal Prince Alfred Hospital in a recent eighteen months' period, there were 30 subjects with aneurysms, an incidence of 3·7%. Unruptured aneurysms, symptomless during life, and found only at autopsy, had an incidence of 1·3%. In other words, in one-third of the cases the aneurysms were unruptured and produced no symptoms. This finding is even more significant when it is considered that over 50% of the 800 autopsies were performed either on babies or on adults whose cranial contents were not examined.

In the whole series of 182 cases, 217 aneurysms were found, the aneurysms being multiple in 14·3% of cases, which figure corresponds with that of Dandy (1944), who found them to be multiple in 15%. Nevertheless, the true figure is probably much higher, for in the 47 subjects inspected by myself in the present series there was an incidence of multiplicity of 25·5%.

The largest number of aneurysms found in any one case was seven—three aneurysms on the right middle cerebral artery and two on the left, one at the bifurcation of the basilar artery and a ruptured aneurysm on the anterior communicating artery.

An aneurysm, being a localized dilatation of an artery, should not be confused with a state of "ectasia", which is a diffuse dilatation involving a considerable length of the vessel. The cerebral arteries in common with vessels in other parts of the body undergo progressive dilatation with age. An ectatic basilar artery often shows tortuosity, and together with one vertebral artery, usually the left, forms an S-shaped curve, which may even produce pressure symptoms on cranial nerves (Dandy). Dandy appears to have included a number of cases showing this deformity in his series of aneurysms, although in reality there should be no confusion between the two. They may, however, occur together.

Site

Saccular aneurysms occurred mainly in the fork of a bifurcation of fairly large vessels. There were none on intracerebral vessels. They were equally distributed on either side of the mid-line.

The site of aneurysms was recorded in 206 cases; 61% occurred on the "internal carotid-middle cerebral" system and 23% in relation to the anterior communicating artery (Figure I). If the circle of Willis is divided into anterior and posterior parts by a line through the

[1] Received on March 18, 1954.

posterior communicating arteries (interrupted line, Figure I), 87·3% occurred on the anterior and only 12·7% on the posterior half of the circle.

Those occurring on the middle cerebral artery mainly arose at the bifurcation, which usually took place about two centimetres from the origin of that artery. In this situation they were slightly more frequent on the right side. Those on the internal carotid were

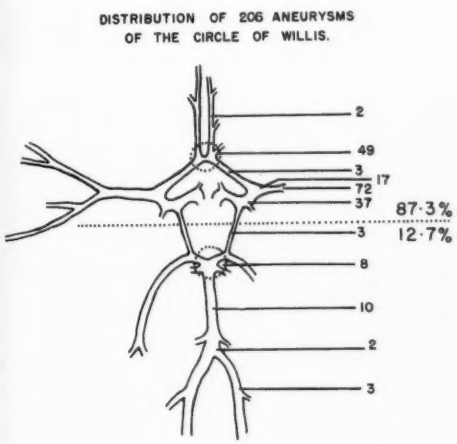

FIGURE I

Diagram of the circle of Willis showing the distribution of aneurysms. Interrupted line divides the circle into an anterior and posterior segment

usually either at its bifurcation, or on the distal side of the junction of the trunk with the posterior communicating or the anterior choroidal artery. Only one aneurysm was found arising from the cavernous portion of the internal carotid artery.

MACROSCOPIC APPEARANCE

Most of these aneurysms were less than one centimetre in their largest diameter, and when small tended to be dome-shaped (Figure II). At first sessile (Figure III), with growth the fundus stretches more quickly than the attachment to the intact arterial wall at its base, and owing to this disproportionate growth, a neck will form. Although the vessels from which the aneurysms arise are only two to four millimetres in diameter, enlargement of the attachment to the artery is possible in a longitudinal direction, so that the neck becomes quite large by comparison with the size of the parent vessel.

After the aneurysm has formed, its growth will depend on the weakness of various parts of the wall. Secondary dilatations may form, giving it a bilocular or even a nodose appearance. These secondary outgrowths, if arising near the fundus of the primary sac, usually contain thrombus. For that matter most aneurysms over eight to 10 millimetres in diameter contain laminated thrombus.

Some aneurysms may enlarge over a period of years to form excessively large sacs of laminated blood clot, and so act as "space-occupying lesions". There were eight aneurysms in this series greater than three centimetres in diameter. The largest of these measured 7·8 by 7·0 by 6·2 centimetres and was thought to have arisen from the internal carotid artery, but dissection and accurate localization in such cases are extremely difficult. This particular aneurysm is one of the largest ever recorded.

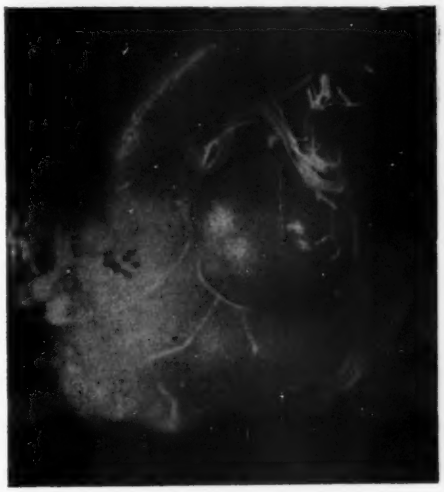

FIGURE II

Dome-shaped aneurysm of the middle cerebral artery arising in the fork of a bifurcation. (×9)

MICROSCOPIC STRUCTURE

At the neck of the aneurysm, both the muscle and the internal elastic lamina usually come to a fairly abrupt end, but either may continue folded back on itself for a short distance into the base (Figure IV).

In the earlier stages the aneurysmal wall consists of cellular fibrous tissue. In the more mature forms the wall is composed of dense hyaline, relatively acellular, fibrous tissue (Figure V). In places there may be a few raised plaques and calcification may occur (Figure VI). This calcification is often irregular in distribution, a fact which is of importance, as radio-

logical evidence of calcification does not signify healing and cannot preclude a weak area through which rupture may eventually occur.

FIGURE III

Saccular aneurysm of the internal carotid artery showing the wide neck. (×9)

RUPTURE OF THE ANEURYSM

When rupture occurs, the vast majority of aneurysms bleed freely and directly into the subarachnoid space. Apart from trauma, the

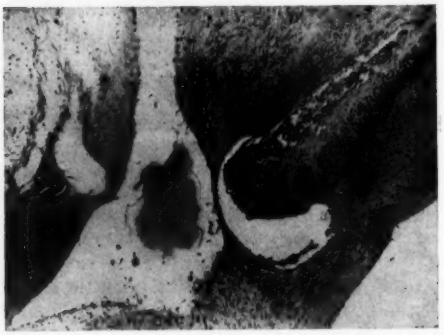

FIGURE IV

Entrance of aneurysm showing abrupt termination of muscle and elastic tissue on each side (Verhoeff's elastic stain). (×48)

two commonest causes of subarachnoid bleeding are ruptured intracranial aneurysm and true cerebral apoplectic hæmorrhage. It is, of course, more profuse and more widespread with a ruptured aneurysm.

Occasionally the aneurysm is embedded in brain tissue and consequently ruptures intracerebrally or directly into a ventricle, with the production of no subarachnoid bleeding apart from that which may leak from the ventricular system into the *cisterna magna*. In some cases there are small repeated hæmorrhages from the aneurysm and symptoms are then less dramatic.

An aneurysm had ruptured in 151 subjects of this series. Of these subjects, 57 (37·7%) showed ventricular hæmorrhage and cerebral hæmorrhage, 13 (8·6%) ventricular hæmorrhage with minimal cerebral hæmorrhage and 24 (15·9%) cerebral haemorrhage alone. Thus,

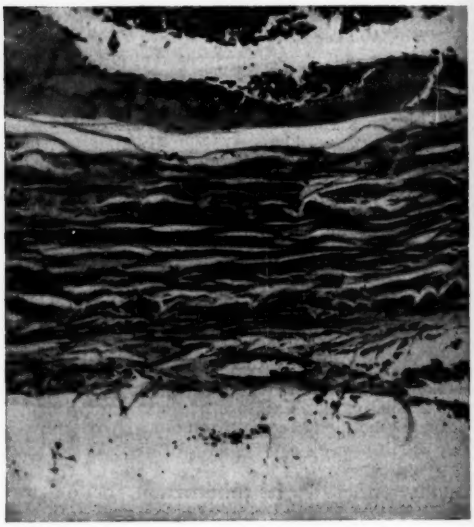

FIGURE V

Wall of aneurysm, consisting of dense hyaline fibrous tissue. The lumen is at the top of the photograph. (Hæmatoxylin and eosin.) (×150)

apart from a minor degree of hæmorrhagic softening, in 62·2% of the cases the aneurysm had bled into the brain to some extent. The commonest sites for this to occur were in the frontal and temporal lobes or both. In smaller series of previous authors the figures have varied somewhat. Richardson and Hyland (1941) reported intracerebral hæmorrhage in 19 (70%) of 27 cases of ruptured aneurysm, and Hammes (1944) in 26 (49·5%) of 53 and Robertson (1949) in 54 (60%) of 90 cases of non - inflammatory aneurysms. Subdural hæmorrhage is known to occur with a ruptured aneurysm, and in this series it was present in 25 cases.

The blood in the subarachnoid space sets up aseptic meningitis, with a mild inflammatory

response. This has been referred to by Jackson (1949) as hæmogenic meningitis. As Bagley (1928), Hammes (1944) and Jackson have shown, polymorphonuclear cells predominate in the early stages, but are rapidly superseded by lymphocytes and macrophages filled with altered blood pigment. Some organization may result, and this fibrosis, by obliterating the subarachnoid space in some cases, results in a communicating type of internal hydrocephalus.

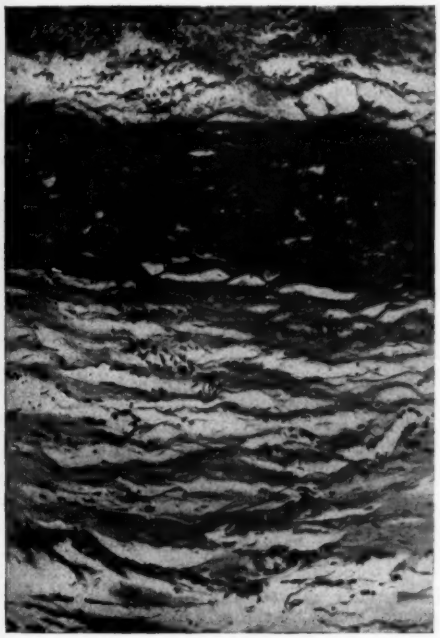

FIGURE VI

Wall of aneurysm with calcification, showing as a heavily stained zone towards the inner aspect of the wall (top of photograph). (Hæmatoxylin and eosin.) (×150)

AGE DISTRIBUTION

As recently as 1952, Forbus stated that "subarachnoid hæmorrhage is characteristically a lesion of young persons, usually under 40 years" and that "typical apoplectic hæmorrhages occur in persons beyond the age of 40, the majority around the age of 60 and beyond".

In the present series of 182 subjects, the age was stated in all but two, and one of these had been an inmate in an old folks' home. The arithmetic mean age was 49·9 years, and contrary to the statement by Forbus (1952), only 26·4% of hæmorrhages occurred within the first forty years of life (Figure VII).

The age incidence of ruptured aneurysm was compared with that of a series of 353 cases of cerebral hæmorrhage already referred to. It was found that the arithmetic mean age was

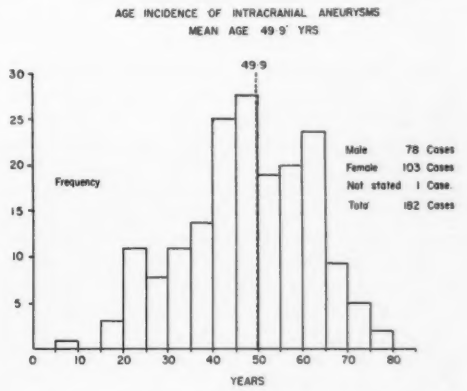

FIGURE VII

The age incidence of cerebral aneurysm

56·4 years (Figure VIII), only 6·5 years older than that for ruptured aneurysms. It can be seen that these two diseases have an age incidence not so far apart as is usually supposed.

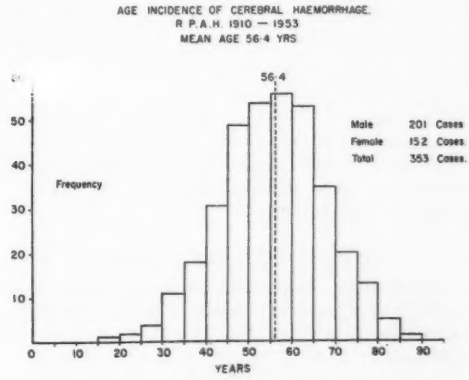

FIGURE VIII

The age incidence of cerebral hæmorrhage

From these figures it must be concluded that the age incidence can no longer be used as evidence in favour of the "congenital theory" of the development of aneurysm, for it is not a disease primarily of young people.

SEX INCIDENCE OF CEREBRAL ANEURYSMS

In this series, the sex was not recorded in one case, and of the remaining 181 subjects, 78 were males (43·1%) and 103 were females (56·9%).

The ratio of males to females differs so much in various series reported in the literature, both in this and in the last century, that the predominance of females here reported is considered of doubtful significance.

HYPERTENSION

The incidence of hypertension associated with aneurysm is well known, but usually not expressed numerically.

The blood pressure of a patient admitted to hospital with subarachnoid hæmorrhage and an associated acute rise in intracranial pressure may be misleading, for this increased pressure is said sometimes to produce a rise in blood pressure. For this reason an attempt was made to determine the incidence of preexisting hypertension mainly from autopsy findings.

The post-mortem examination was limited to the cranial cavity alone in 26 cases of the 182, so these were excluded.

Of the remaining 156 subjects, it was considered that 89 (57%) had preexisting hypertension. This figure of 89 was made up of two groups. In the first (77 cases), there was left ventricular hypertrophy. The 12 subjects in the second group each had two of the following criteria: (i) a heart weighing more than 420 grammes if a male, and 400 grammes if a female; (ii) granular contracted kidneys; (iii) a blood pressure in which both the systolic exceeded 150 millimetres of mercury and the diastolic 90 millimetres.

This figure of 57% is probably very conservative and is considered to indicate that the incidence of hypertension in cases of intracranial aneurysms is somewhat higher than in the general community.

CONGENITAL ABNORMALITIES

Apart from coarctation of the aorta and perhaps polycystic disease of the kidneys, congenital abnormalities do not appear to be significantly more frequent with aneurysms.

In this series there were four cases of coarctation of the aorta and two of polycystic disease of the kidneys. This association, if significant, is considered as primarily due to the hypertension occurring as a concomitant to these two conditions.

SUMMARY

A general survey of intracranial arterial aneurysms of non-inflammatory nature is presented and their frequency emphasized.

A series of 182 cases of aneurysms, proved by autopsy, has been collected. The aneurysms were multiple in 14·3%, and 87·3% occurred on the anterior half of the circle of Willis.

Their microscopic and macroscopic appearance is described, and it is stressed that the aneurysms have a wide base or neck, in comparison with the size of the parent vessel.

The various sites of hæmorrhage from rupture of the aneurysms are discussed, and there is an incidence of significant intracerebral hæmorrhage in 62·2% of the cases.

The age incidence of aneurysms in this series was 49·9 years, compared with 56·4 years for 353 cases of true cerebral apoplectic hæmorrhage. As aneurysm is not predominently a disease of young persons, the age incidence can no longer be used as evidence in favour of the "congenital theory" of their development.

Hypertension was estimated as being present in 57% of cases, which is considered significantly high.

ACKNOWLEDGEMENTS

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A FOLLOW-UP OF CASES OF PLUMBISM IN CHILDREN[1]

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As part of a wider investigation into the ætiology of " chronic nephritis " in Queensland, a follow-up of children who had lead poisoning between the years of 1915 and 1935 has been carried out. It was decided to report the follow-up separately in view of its somewhat striking results and the recent interest in lead poisoning in children.

HISTORICAL SURVEY

Lead poisoning in Queensland was first reported in 1892 by the medical staff of the Brisbane Children's Hospital, who described a number of cases in which limb pareses were present (Gibson *et alii*, 1892). At the same time, Turner (1892) gave an account of four cases in children of " probably localized basal meningitis " ; the patients had " optic neuritis accompanied by paralysis of one or both external recti, by headache, sometimes by vomiting, sometimes by retraction of the head ", but Turner did not associate the condition with lead poisoning. Five years later, two papers, one by Turner (1897) and the other by Gibson (1897) gave reasons for ascribing this clinical picture to plumbism, and described two other manifestations — " cases characterized by abdominal pain and pain in the limbs " and " eclamptic convulsions ". This is the first description of lead encephalopathy in children.

The *Australasian Medical Gazette* of 1899 contains a short review of the diagnostic clinical features of lead poisoning in childhood by Turner, and later a paper was published by Gibson (1904) describing the results of investigations which indicated that veranda railings and other structures painted with lead-containing paint were the source of plumbism in Queensland children. This commenced a campaign by the Queensland Branch of the British Medical Association for legislation prohibiting the use of lead paint. In 1909 the clinical features of plumbism in childhood were again reviewed by Turner, and a careful study, including estimations of lead in urine and fæces, of a series of cases was published by Breinl and Young in 1914.

Legislation prohibiting the use of lead paint was pending in Queensland in 1922, when evidence was given by a physician from Sydney, New South Wales, before a public inquiry into the hazards of white lead in paint, to the effect that the ingestion of lead paint by children could not cause clinical poisoning (Smith, 1921). This provoked rebuttals by the Council of the Queensland Branch of the British Medical Association (1922) and by the Board of the Hospital for Sick Children, Brisbane, among others. The legislation became law in 1922 ; but its implementation was slow and it was not until the late 1930's that plumbism ceased to be a problem in children in Queensland.

The diagnosis of lead poisoning in Queensland children and its relation to chronic nephritis is further discussed by Nye (1929, 1933) and Murray (1939).

TABLE I

Sex and Age (Next Birthday) of Subjects of Lead Poisoning at Time of Admission to Hospital, 1915 to 1935

Age (Years)	Males	Females	Total
2	17	18	35
3	20	42	62
4	33	51	84
5	26	38	64
6	17	27	44
7	13	16	29
8	9	16	25
9	15	9	24
10	11	4	15
11	7	11	18
12	1	—	1
Total ..	169	232	401

THE SERIES

The series comprises 401 children who were in the Hospital for Sick Children, Brisbane, with a diagnosis of lead poisoning, between the years 1915 and 1935. Their sex and age at the time of admission to hospital are shown in Table I. The number of admissions to hospital in each of the years from 1915 to 1935 is contained in Table II.

METHOD

The follow-up was conducted mainly through the records of the Registrar-General of Queensland and the Electoral Office of Queensland,

[1] Received on March 22, 1954.

TABLE II

Number of Admissions Each Year (1915 to 1935) and Number of Subjects Who Later Died of Renal or Vascular Causes

Admissions and Deaths	Year																					Total
	1915	1916	1917	1918	1919	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	
Number of admissions	8	27	32	24	36	27	23	28	40	45	9	35	12	9	12	14	6	6	4	2	2	401
Number of deaths[1] ..	1	8	14	7	9	13	10	8	10	10	2	6	2	2	2	1	2	—	1	—	—	108

[1] Deaths in later years due to chronic nephritis, nephritis unspecified, other renal sclerosis, essential malignant hypertension, nephrosclerosis and cerebral hæmorrhage.

and is as complete as possible up to December, 1953. The birth certificates of the children concerned were first found for purposes of identification, and the marriage register was checked for change of name of the females. The register of deaths was searched and then the electoral roll was checked for the names of those not on the death register. A circular requesting details of present health was sent to the electoral addresses, and those who agreed were medically examined. In addition, family doctors were written to and the records of the Brisbane General Hospital, the Mater Misericordiæ Public Hospital, the Ipswich General Hospital and Commonwealth Pensions Office were searched.

RESULTS

Some information was obtained about 352 of the children and none about the remaining 49. These 49 are retained in the series because it is known that they have not died in Queensland, and although they may have died in other States, they are probably still alive.

Of these 352, death certificates were seen for 101 females and 64 males, five war deaths being included—a total of 165. All the deaths occurred between the ages of one and forty years. This mortality rate for the whole series of 396 (excluding war deaths) is 40,404 per 100,000. The average annual mortality rate from all causes in the general population of Queensland between the ages of one and forty years for the years 1928 to 1937 inclusive was 263 per 100,000.

Deaths

The causes of deaths in the certificates were classified according to the International Classification of Diseases, Injuries and Causes of Death, sixth revision, adopted 1948. When plumbism and chronic nephritis appear on the same certificate, the condition has been classified under chronic nephritis, provided that the death occurred at least five years after the hospital admission for plumbism. Malignant hypertension was not specified as essential on the two certificates concerned, although it was classified as such.

The classification of the causes of death is given in Table III, and the sex and age at death in Table IV. The deaths of 66 females and 42 males, a total of 108, are classified under chronic nephritis, nephritis not specified, other renal sclerosis, nephrosclerosis, essential malignant hypertension and cerebral hæmorrhage. This represents a mortality from these causes for the whole series of 26,932 per 100,000. The average annual mortality from chronic nephritis, nephritis unspecified and cerebral hæmorrhage in the general population aged

TABLE III

Causes of All Deaths

Class Number	Cause of Death	Number of Cases
592	Chronic nephritis	94
593	Nephritis unspecified	4
594	Other renal sclerosis	3
331	Cerebral hæmorrhage	1
441	Essential malignant hypertension ..	2
446	Nephrosclerosis	4
055	Diphtheria	3
002	Tuberculosis (pulmonary)	1
050	Scarlet fever	1
056	Pertussis with pneumonia	1
080	Anterior poliomyelitis	1
201	Hodgkin's disease	1
309	Dementia	1
343	Encephalitis	2
353	Epilepsy	3
401	Acute rheumatism	1
421.4	Chronic endocarditis	2
493	Pneumonia (no organism specified) ..	2
570	Intestinal obstruction	1
571	Gastroenteritis	1
572.2	Ulcerative colitis	1
600	Chronic pyelonephritis	2
642	Acute nephritis of pregnancy	1
688.2	Sudden death in puerperium	1
692.6	Cellulitis (no organism specified) ..	1
780	Convulsions	3
790.2	Depression	1
E812	Motor-car accident	2
E843	Fall from bicycle	1
N966	Lead poisoning	17
N991	Strangulation (suicide)	1
	War death	5
	Total	165

from fifteen to forty years, between the years 1928 and 1937 inclusive, was 36 per 100,000.

The duration of life after the hospital admission for lead poisoning of patients who died of the foregoing renal and cardio-vascular causes is shown in Figure I.

The shortest duration was six years and the longest was 34 years. Seventy-one members of the series died of these causes between ten and twenty-four years after they had lead poisoning. Sex made no difference to the duration of life.

TABLE IV

Sex and Ages at Death from Various Causes (War Deaths Excluded)

Age (Years) and Sex	Causes[1]		
	592, 593, 594, 441, 446, 331	N966	Others
0 to 4:			
Males ..	—	4	—
Females ..	—	7	4
5 to 9:			
Males ..	1	1	5
Females ..	3	3	4
10 to 14:			
Males ..	3	1	4
Females ..	9	1	3
15 to 19:			
Males ..	9	—	2
Females ..	16	—	4
20 to 24:			
Males ..	11	—	1
Females ..	15	—	2
25 to 29:			
Males ..	11	—	3
Females ..	16	—	2
30 to 34:			
Males ..	2	—	—
Females ..	4	—	—
35 to 39:			
Males ..	2	—	—
Females ..	6	—	1
Total ..	108	17	35

[1] 592, chronic nephritis; 593, nephritis unspecified; 594, other renal sclerosis; 441, essential malignant hypertension; 446, nephrosclerosis; 331, cerebral hæmorrhage; N966, lead poisoning.

The validity of the diagnosis of chronic nephritis must be admitted. The disease is one of long duration and is usually diagnosed a considerable time before death. The clinical picture is well known to practitioners in Queensland, where the disease is very common, and the two main signs of the disease are found by tests that are routine in practice—the measurement of the blood pressure, and testing of urine. In addition, there are no common conditions causing death under the age of forty years which are likely to be clinically confused with chronic nephritis. It is far more likely that some of the more acute manifestations of chronic nephritis may be misdiagnosed as some other condition. For example, it may well be that some of the deaths in this series certified as due to convulsions or epilepsy were actually the result of hypertensive cerebral vascular disease.

There remain 35 deaths, after the subtraction of those due to renal and vascular causes, due to plumbism and to war. This is still far in excess of the mortality to be expected. There are two probable explanations of this fact.

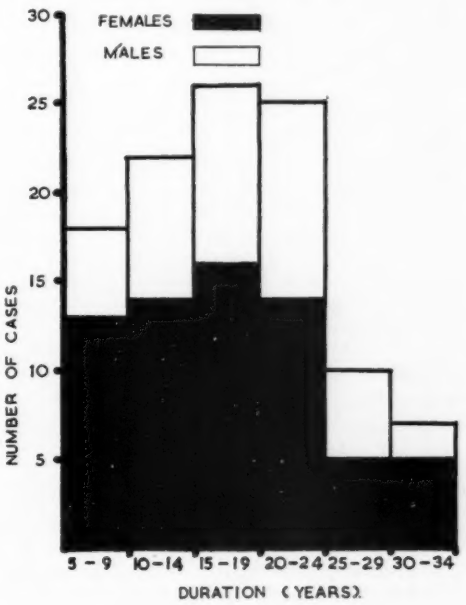

FIGURE I

Duration of life from hospital admission for lead poisoning until death from cardio-vascular and renal disease

Firstly, many of the causes of death could represent sequelæ of plumbism. This category would include dementia, encephalitis, epilepsy, convulsions, depression, strangulation (suicide), all of which may arise from brain damage, and chronic endocarditis, acute nephritis of pregnancy and sudden death in the puerperium, which may be manifestations of hypertension and renal disease. Secondly, the high death rate from infective causes may be due to the fact that plumbism in children produces chronic ill-health which could be associated with a decreased resistance to infection. All such

deaths occurred within three years of the plumbism. The causes of the war deaths could not be determined.

Living Members of the Series

One hundred and eighty-seven members of the series are known to be alive and on the electoral roll. Information on the state of health of 101 of these has been obtained by one or more of the means mentioned above.

Seventeen of these have hypertension and albuminuria and three have hypertension alone, a blood pressure of over 140 millimetres of mercury, systolic, and 90 millimetres, diastolic, after rest, being taken as representing hypertension. Thus a total of 128 members of the series, including those dead, have had renal or vascular disease.

Five of the 101 are mentally defective to the extent of being unable to make their own living. In addition, mental deficiency is mentioned on two of the death certificates. It is impossible, however, to draw any conclusions as to the causal relationship of plumbism to mental deficiency, as nothing is recorded of the mentality of those children before their plumbism, and it is possible that a mentally defective child would be more likely to acquire it than a normal one.

Three of the 101 have psychoses severe enough to necessitate their confinement in a mental hospital.

Two have been blind since the initial illness and have complete optic atrophy.

The Original Diagnosis of Lead Poisoning

Considerable difficulty arises in establishing the correctness of the original diagnosis in a follow-up such as this, in which the original diagnosis was made many years ago by persons other than the one who is conducting the follow-up.

The absolute correctness of the diagnosis of lead poisoning in all the cases of this series cannot be proved, but the evidence available at present relating to it will be presented. Such evidence is available from three sources—the publications of the men who made the diagnosis, the records of the cases in the series, and the lead content of bones of members of the series who have died recently.

The criterion for inclusion of an individual in this series was that he had been listed in the records of the Hospital for Sick Children, Brisbane, as having had lead poisoning, the diagnosis having been made by the visiting physician at the time. The high professional calibre of these physicians can be judged from their articles mentioned in the first section of this paper, and there can be no doubt that they had an accurate knowledge of the clinical picture of lead poisoning in children. The clinical descriptions contained in the articles could scarcely be bettered today. Plumbism in children was a constant source of discussion in the Queensland medical community, particularly as its members had to defend the diagnosis against their somewhat sceptical colleagues from the southern States of Australia. Plumbism in children did not occur to any extent outside Queensland, because the type of house elevated on stumps, with large verandas and painted railings which acted as a source of lead, is peculiar to that State.

The Hospital for Sick Children, Brisbane, did not become a teaching hospital until 1939, and the clinical notes in many of the records of members of this series were incomplete and inadequate. A preliminary analysis of the records was carried out in 1949 by Dr. Irene Phillips (then Nash), of the Department of Pathology, University of Queensland. Dr. Phillips made a note of the records which contained unequivocal signs. There were five groups of these signs: (i) encephalopathic signs including papillœdema, external ocular paresis and convulsions; (ii) bilateral limb paresis; (iii) blue line on the gums; (iv) lead in the urine in excess of 0·1 milligramme per litre; (v) punctate basophilia in the red blood cells. Records of such signs were found in 125 of the 401 cases. In the remainder, either the clinical picture was of the type in which there are no definite signs, the patient suffering from colic, anorexia, vomiting, irritability, loss of weight, constipation and pain in the limbs, or the records were inadequate.

Of the groups of signs, group (i) was present in 34 records, group (ii) in 115, group (iii) in 51, group (iv) in 15, and group (v) in 79. One patient had all five groups, six patients had four, 45 had three, 57 had two and 15 had one. Of this last 15, three had group (i) signs, and 12 had group (ii) signs. The lead content of the urine was estimated infrequently. No record was made of those cases in which basophilia and blue line were the only signs in addition to symptoms. Dr. Phillips was unable to complete the survey, and most unfortunately the records themselves were destroyed in 1950, so it has been impossible to obtain any information about the diagnosis other than that already given.

Forty-four of these 125 patients have had renal or vascular disease—a rate of 35%. Eighty-four of the 276 members of the series, about whose attacks of lead poisoning no

detailed information is available, have had renal or vascular disease—a rate of 30%. These rates suggest that the two groups are essentially similar in the ætiology of the renal and vascular disease.

Thirty-eight members of the series agreed to medical examination. All of the 38 or their parents could remember the lead poisoning. The memory of details was, of course, vague, but the general pattern of symptoms was clear. The following are some examples of the type of description: "He was sick for a long time with dry retching, then his legs began to go weak." "I remember seeing double at school, then I had a fit." "My legs were in irons for six months." There were no descriptions inconsistent with lead poisoning.

Of the 38, eight had had an extract of the original records made as above. The histories given by all these corresponded with the recorded signs.

Thirty-five of the 38 had a clear memory of the houses in which they spent their infancy. All the houses had verandas with painted railings.

None of the 38 had had "kidney trouble" in childhood, and none could remember any illness with symptoms suggestive of acute nephritis. All had had some of the exanthemata of childhood, but the memory of which ones was so vague that the information was of no value.

Lead poisoning was the only definite illness common to all. As far as residual signs of the original disease were concerned, two subjects were blind, with complete optic atrophy, and four had well-marked bilateral *pes cavus*. Another patient, in addition to bilateral *pes cavus*, had patchy wasting of the thigh muscles, suggesting that the original condition was poliomyelitis, not lead poisoning.

Meagre but suggestive evidence of the correctness of the original diagnosis of lead poisoning is available from estimation of the lead content of bone after death. Samples of bone have been obtained from two members of the series who have died during the past two years. The samples were taken from the calvarium and from the sixth left rib in the anterior axillary line. If the lead content is expressed in milligrammes per 100 grammes of moist bone, the findings were as follows: In Case I the subject, a female, had 5·6 milligrammes in the rib and 10·0 milligrammes in the skull. In Case II the subject, also a female, had 2·5 milligrammes in the rib and 7·1 milligrammes in the skull. The values for persons under the age of forty years dead from causes other than chronic nephritis are as follows: rib, 1·1 milligrammes, standard deviation 0·8 milligramme; skull, 1·9 milligrammes, standard deviation 1·3 milligrammes.

Both these subjects were in the group whose records were vague or inadequate. Neither of the two had a history of industrial exposure. Both died of chronic nephritis. The possibility that chronic nephritis causes a retention of normally ingested lead has been investigated and rejected. This will be discussed further in another paper.

With regard to the possibility that renal disease was originally misdiagnosed as lead poisoning, Dr. Phillips states that, although it was looked for, there was no evidence in the original charts to suggest this. A number of the subjects had albuminuria. Turner (1909) made the following statement: "Transitory albuminuria is not uncommon. Chronic interstitial nephritis is, I believe, an occasional but rare complication." The account of lead poisoning among Queensland children endorsed by the Council of the Queensland Branch of the British Medical Association (1922) states: "There is a strong impression among some Brisbane practitioners that the prevalence of chronic nephritis among young adults in this city is partly a late result of absorption of lead during childhood. To prove this would be very difficult and in the absence of proof it can only be regarded as a probable opinion." These statements by the men who were responsible for making the diagnosis of lead poisoning in this series leave little doubt that there was no confusion in their minds between plumbism and renal disease in childhood. The second paper mentioned also contains an account of the clinical features of 12 cases then in the Brisbane Children's Hospital, which would be included in the present series.

Summary

A follow-up was made of 401 children, who were in the Hospital for Sick Children, Brisbane, between the years 1915 and 1935 with a diagnosis of plumbism.

One hundred and sixty-five are known to be dead and 187 to be alive, and nothing is known of the fate of the remaining 49.

One hundred and eight of the causes given on the death certificates were classified as being renal or vascular disease.

Seventeen of the living members have hypertension and albuminuria and three have hypertension alone.

The evidence available indicates that the original diagnosis of plumbism was probably correct in the majority of the cases.

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THE ELIMINATION OF LEAD IN SWEAT[1]

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IN contrast to the very large amount of work which has been done by numerous observers on the elimination of lead in the urine, very little has been done on the problem of elimination of lead by the skin. Further, the small amount of work which has appeared was done when analytical methods were not so sensitive as they are now. Since the volume of fluid eliminated by the skin in conditions of moderate temperature may equal that of the urine, and in hot conditions may greatly exceed it, the probelm is of considerable importance.

PREVIOUS WORK AND OPINIONS

Although some of the earlier investigators (Du Moulin, 1884; Oliver, 1914) considered that lead was excreted in the sweat, more recent opinion appears to have been against this view, or at any rate against the view that such elimination was of any importance.

Du Moulin (1884) held that lead was eliminated in the sweat. Lavrand (1886), discussing Du Moulin's work, stated that lead was eliminated in the bile, little or not at all by the urine, and not at all by the skin. He stated definitely that the skin did not absorb lead and did not eliminate it. He considered that the lead which he detected on the skin was due to surface contamination from an external source, as after complete washing lead did not reappear on the skin, but iron did to a slight extent, coming from decomposition of hæmoglobin.

In contrast with Lavrand's views, Oliver (1914) made the following statement: "It [the skin] is, however,a surface by which lead may be eliminated from the body. In some of my hospital patients Professor Bedson found lead in the perspiration."

His reports of his experiments on the electrolytic method of removing lead through the skin, while not conclusive (since no results of analysis for lead of the salt used in the electrolytic bath were given), are at least suggestive that lead can be eliminated via the skin. Lead was found in the water of the electrolytic bath and on the electrodes, not only in cases of plumbism due to inhalation of dust, but also in the case of a woman with lead poisoning, not caused by occupation, but due to excessive lead in drinking water. It was not made clear whether steps were taken to ensure that surface contamination due to bathing in the same water could not have contributed to the result.

Legge and Goadby (1912) made the following statement: "The two chief channels of elimination are the urine and fæces while some include the saliva and sweat. In the case of the sweat there is not much evidence, but a few observers, mainly French, claim to have discovered traces of lead in the skin of lead workers. Although brisk peripheral circulation and transudation may possibly carry off a certain amount of lead, the chance of this is highly improbable."

Aub *et alii* (1927), in discussing the sulphuretted hydrogen test for lead on the skin, stated that with the passage of time the degree of coloration of the skin by sulphuretted hydrogen becomes less "an indication that the lead present soon after exposure is merely contamination and has not been excreted". They stated that possibly lead was excreted to a slight extent by the skin.

Cantarow and Trumper (1944) made the following statement: "The observation of early investigators which suggested that lead is excreted by the skin may be regarded as of purely historic interest. Oliver is among the few modern authorities who has reported the presence of lead in the perspiration. The majority regard this as improbable and are inclined to attribute such findings to contamination of the surface of the skin with lead, the possibility of which can scarcely be eliminated in lead workers." Cantarow and Trumper stated that lead might possibly be excreted to a slight extent by the skin.

To adduce as did Aub *et alii* (1927) the gradual diminution of the degree of coloration as evidence of mere external surface contamination is extraordinary, since a gradual diminution is just what would be expected if the lead was being excreted. Even if the skin was not washed at intervals, the contact with clothing or other materials would gradually remove any lead which had accumulated on the skin from the evaporation of the sweat in which it had been excreted. The amount excreted would be

[1] Received on February 19, 1954.

expected to diminish gradually, a gradual diminution of the amount of lead in the urine being just what happens after removal from exposure, and there is no reason to suppose that this does not happen in other body fluids also, such as the sweat.

It would appear that there has been little experimental work done, at any rate in recent years. The opinions of a few earlier experimenters and writers have been accepted too readily.

It must be remembered that analytical methods for the detection of lead are much more sensitive now than they were in the eighties, when Du Moulin and Lavrand wrote. The latter's statement referring to cases of lead poisoning, that lead was eliminated " little or not at all by urine ", indicates that the analytical methods he used were not sensitive enough and quite inadequate even to detect lead in the urine, and still less adequate to detect it in small amounts of sweat, or collected in small amounts on the skin, after it had been cleansed from external contamination.

PRESENT WORK

This paper records the results obtained with seven subjects; six were suffering from lead poisoning, and the other was a sedentary worker with no significant exposure to lead.

Method

A pad of cotton wool approximately eight centimetres by six centimetres in area was attached to the skin of the chest wall in the axilla by means of plastic or adhesive tape. The pad was backed by " Cellophane " to prevent contact of the tape with the pad.

The axillary region was, of course, carefully washed before the application of the pad, and the hospital subjects all wore clean hospital clothes; one industrial subject not in hospital wore clean non-working clothes.

The pad was left in position for several days. It was then removed, the cotton wool was separated from the " Cellophane " backing and then treated with dilute nitric acid, and the lead content was determined by the dithizone method.

Blank determinations for lead were made in all cases by the use of control pads of similar size from the same sample of cotton wool, and the same volume of reagents as were used for the sweat pads.

The amount of lead taken up by the pad in each case was obtained by subtracting from the total amount of lead found that in the control pad and reagents, which in all cases was small relative to the total amount of lead.

The final comparisons were made by the " one colour " method in a photoelectric colorimeter. In one case, the last, the determination was also made by the " mixed colour " method as well, visual comparison being used. The values by the two methods agreed very well.

LEAD IN SWEAT OF PERSONS SUFFERING FROM LEAD POISONING

In two cases, owing to the advised routine not being followed, the pad was attached by adhesive tape (not the clear plastic type), but still across the " Cellophane " backing. In one of these cases the " Cellophane " developed a crack, across which was the adhesive tape.

In order to overcome any contamination of the pad by lead from the adhesive tape, this pad was split horizontally and the outer half was discarded and not analysed.

Adhesive tape of similar type was analysed for lead. A piece 10 centimetres by five centimetres in area yielded 0·04 milligramme of lead. Considering that the part in contact with the pad through the cracked " Cellophane " would not be greater than three centimetres by one centimetre in area, the contamination due to the tape would probably not exceed 0·0025 milligramme.

Table I shows the results obtained; it also includes some blood lead concentrations, the urinary lead concentration and the total urinary lead excretion, the latter for the period during which the pad was worn. The values for the lead found on the pad are the values found after allowance has been made for that found in control pad and reagents.

Inspection of Table I shows that the lead on the pads represented a considerable amount relative to the total amount excreted in the urine during the time when the pads were in position.

Great care was taken with the reagents and in the analytical methods. The analysts had all had considerable experience in determining small amounts of lead in urine, blood and air. It can be accepted that the sweat pads which had been worn by the lead-poisoned subjects (B, L, M, F, Y, C) contained very significantly greater amounts of lead than the control pads of the same sample of cotton wool which were not worn, and than the pad worn by S in the colder month (April). This, of course, does not settle the question of possible external contamination in the lead poisoning cases.

However, it is not considered likely that external contamination was the source of the lead found on the pads in these cases of lead poisoning.

TABLE I

Excretion of Lead in Urine and Sweat by Patients Suffering from Lead Poisoning

Subject	Date	Period of Collection of Sweat (Days)	Time Since Last Exposure to Lead, when Pad Applied	Blood Lead Content (Milligrammes per 100 Millilitres)	Total Lead in Urine for Period of Pad (Milligrammes)	Total Amount of Lead on Pad (Milligrammes)	Lead Excreted per Day in Sweat (Milligrammes)
B.							
On citrate therapy from 21/3/52	4 to 7/4/51	3	16 days	0·21	1·12	0·1	0·03
	7 to 8/4/51	1	19 days	0·19	estimated 0·28	0·01	0·01
M.							
Started thiosulphate therapy every second day on 27/6/52	24/6 to 1/7/52	7	11 days since last exposure, which lasted only 4 days	0·24	1·09	0·165	0·0235
L.							
Started thiosulphate therapy (half dose) on 26/7/52	23 to 28/7/52	5	3 days	—	1·78	0·07	0·014
F.							
Thiosulphate on 17/9/52, 21/9/52, 23/9/52	15 to 17/9/53	2	4 days	0·19 on 11/9/53	0·30	0·092 (right side)	0·046
						0·036 (left side)	0·018
	18 to 23/9/53	5	7 days		0·489	0·024 (right side)	0·0048
						0·008 (left side)	0·0016
Y.							
On thiosulphate therapy daily from 17/10/53	16 to 19/10/53	3	14 days	—	—	0·01	0·0033
	19 to 21/10/53	3				0·018	0·0060
	22 to 25/10/53	3				0·040	0·0133
C	16 to 19/10/53	3	—	—	—	0·0444	0·0148
On thiosulphate therapy daily from 16/10/53	19 to 21/10/53	3	—	—	—	0·028	0·009
	22 to 25/10/53	3	—	—	—	0·020	0·007
S.	April, 1951	3	No exposure	—	—	0·00	0·000
	October, 1953	3	No exposure	—	0·13	0·012	0·004
	October, 1953	3	During ingestion of lead	—	0·17	0·024	0·008
	December, 1953	3	During ingestion of lead	—	—	0·050	0·017

There are two facts which strongly support this view. The first is that in several of the cases a considerable time had elapsed between the cessation of exposure and the application of the pads (16, 19, 11, 14 days).

Admittedly, the skin of a person exposed to lead dust may quite likely have a certain amount of lead on it, or in the pores; but in the case of persons of reasonably clean habits it is unlikely that this surface contamination in the axillary region would be of significance sixteen days after removal from exposure to lead, and after preparation of the area by a nursing sister.

The second fact is that in the case of subject Y, who had had heavy exposure, but on whom the first pad was not applied until at least fourteen days after his leaving work, and who was given daily injections of sodium thiosulphate (an agent known to increase the elimination of lead in urine and fæces) from a time halfway through the wearing of the first pad, the amounts found on the two pads worn for the next two three-day periods showed marked progressive increases. The amounts collected in the three pads were 0·01, 0·018 and 0·040 milligramme respectively.

LEAD IN SWEAT OF PERSON NOT EXPOSED TO EXTERNAL CONTAMINATION FROM LEAD

In order to prove conclusively that lead can be eliminated in significant amounts in the sweat, the following experiments were carried out. The writer wore a sweat pad for three days during cool weather in April. The amount of lead above that in control pad and reagents was nil.

The experiment was repeated in October in warmer weather.

The pad was attached at first with clear plastic adhesive across " Cellophane " backing.

This method of attachment proved unsatisfactory in the case of a person who was going about his ordinary activities. After twelve hours the clear plastic adhesive was replaced by adhesive tape.

Twenty-four-hour specimens of urine were collected during these three days. The amount of lead on the pad was 0·012 milligramme. Several days later he started to take five milligrammes of lead as the acetate daily by mouth. On the third day a pad was attached as in the latter part of the first experiment and

TABLE II

Excretion of Lead in Urine and Sweat by Normal Subject (D.O.S.)

Period	Amount of Lead Taken (Milligrammes)	Volume of Urine in 24 Hours (Cubic Centimetres)	Lead in Urine		Lead in Sweat (Milligrammes per Litre)
			Content in Milligrammes per Litre	Total Lead Content in Milligrammes	
1					
Preliminary three days:					
19 to 20/10/53 First day	None	1205	0·025	0·03	Total for three days, 0·012
20 to 21/10/53 Second day	None	2420 } 5671	0·025	0·06 } 0·13	
21 to 22/10/53 Third day	None	2046	0·02	0·04	
2					
Five days while ingesting lead:					
26/10/53 First day	5	Not collected			
27/10/53 Second day	5	Not collected			
28/10/53 Third day	5	990	0·025	0·025	Total for three days, 0·024
29/10/53 Fourth day	5	1990 } 5220	0·033	0·065 } 0·17	
30/10/53 Fifth day	5	2240	0·035	0·08	
3					
Four days while ingesting lead:					
21/12/53 First day	10	—	—	—	Total for three days, 0·05
22/12/53 Second day	10	—	—	—	
23/12/53 Third day	10	—	0·035	—	
24/12/53 Fourth day	10	—	—	—	
		11 a.m.	0·025	—	
		3.50 p.m.	0·06	—	

remained in position for three days, on each of which five milligrammes of lead were taken. The amount of lead collected on the pad during these three days was 0·024 milligramme. In December, when the weather was warmer still, the experiment was repeated; this time 10 milligrammes of lead were taken daily for four days. The pad was worn from 10 p.m. on the first day on which the lead was taken until 10 p.m. on the fourth day. The amount of lead collected on the pad was 0·05 milligramme.

The results are summarized in Table II.

The amounts of fluid drunk each day during the three tests were very similar.

The climatic conditions during the first two experiments were comparable.

During the third test the temperature on the first day (December 21, 1953) was 95·3° F. and the atmosphere fairly humid. The pad was adjusted at 10 p.m. On the next day the maximum temperature was 76·3° F. On the succeeding day the maximum temperature was 78° F., but humidity was higher and the subject was sweating more freely (so far as visible sweat was concerned). On December 24 the maximum temperature was 80° F. and the subject was sweating more freely still. The pad was removed at 10 p.m. on this day.

The daily output of urine was not measured in the third test, but it was considerably reduced.

There were thus both an increased ingestion of lead and increased sweating, and these were accompanied by a greatly increased amount of lead on the sweat pad.

The results of these tests and of the previous test carried out on subject S in the cool month of April may be summarized in the following statement. The amounts of lead collected on the sweat pads during three-day periods were as follows: (i) no extra lead taken, in cool month of April, 0·000 milligramme; (ii) no extra lead taken in October (warmer weather), 0·012 milligramme; (iii) during taking of 15 milligrammes of lead in the three days in October, 0·024 milligramme; (iv) during taking of 30 milligrammes of lead in the three days in December (warmer weather), 0·050 milligramme.

SIGNIFICANCE OF AMOUNT OF LEAD EXCRETED IN SWEAT

It is not known what fraction the amount of fluid collected on the small pads in the axilla (eight by six centimetres in area) was of the total amount of fluid excreted by the whole body surface; but it must have been small.

The area of the pad was 48 square centimetres. An approximate estimate of the area of the body surface of subject S was 17,000 square centimetres, 354 times as great.

Table III shows the lead collected on the sweat pads as a fraction of the lead excreted in the urine in the same period in those cases in which twenty-four-hour specimens of urine were collected.

Even when allowance is made for the fact that some areas of the skin are more abundantly provided with sweat glands than are others, it is practically certain that the amount of lead excreted by the skin of the whole body surface

was many times that on the pad, probably 50 or 100 times as much. Since the amount excreted on the pad was of the order of one-seventh to one-tenth of that excreted in the same time in the urine, it is obvious that the amount eliminated by the skin may greatly exceed that eliminated in the urine.

TABLE III

Subject	Lead on Pad as Fraction of Lead in Urine
B	1/11
M	1/6
L	1/25[1]
F	1/3 and 1/20
S	1/10 and 1/7

[1] Half of pad discarded.

In order to make a rough estimate of the fraction of the amount of sweat secreted by the total body surface which was collected on the axillary pad, the following experiment was carried out.

A pad of the same size backed with "Cellophane" was weighed and then attached to the skin in the axilla, and the edges were sealed to the skin with plastic adhesive to make an airtight seal. Before the experiment was finished the seal broke away, but since the air in the whole axillary area beneath the clothing was obviously saturated with water vapour, there could have been no loss of water by evaporation from the pad, though there could have been some loss by seepage along the skin surface. Close contact was kept between the pad and the skin throughout the experiment. The day was hot (95° F. shade temperature), and the subject sweated freely. After the pad had been left for three hours and ten minutes, the plastic seals were removed, and the pad was folded over and sealed to prevent evaporation of moisture during manipulation. It was weighed again. The results were as follow: weight before absorption of sweat, 3·6 grammes; weight after absorption of sweat, 4·6 grammes; weight of sweat absorbed, 1·0 gramme.

Assume that 1000 grammes of sweat were secreted by the whole body surface in twenty-four hours. (This is a very conservative estimate under the atmospheric conditions obtaining during the test; the actual amount might have been two and a half to three times this, but the low figure has been taken purposely to give the least favourable view to the results.)

Assume that the sweat was excreted at a steady rate throughout the twenty-four hours. (The amount collected on the pad in twenty-four hours could then be 7·6 grammes.) This would not be strictly true, since during the cooler night less would be excreted than during the heat of the day. The assumption will result in the amount estimated for the axilla in twenty-four hours being greater than the actual amount. Even with these assumptions, which definitely load the evidence in favour of the axilla as a relatively high sweat-producing area, the amount collected on the axillary pad was a very small fraction of the total body sweat—about one-one hundred and thirtieth. It is evident that the quantity of lead eliminated through the skin may be of the same order as, or may even exceed, the amount eliminated in the urine.

In hot climates, owing to profuse sweating, the amount eliminated through the skin may greatly exceed that removed by the urine.

The fact that lead is eliminated in the sweat must always be considered in any assessment of the excretion of lead by sweating animals (including man), either in connexion with such excretion in ordinary circumstances, or during treatment.

SUMMARY

Lead has been found in significant amounts in the sweat of six subjects of industrial lead poisoning, and of one person with no industrial exposure to lead, who ingested lead.

It is considered that the amounts found in the lead poisoning cases were largely due to actual elimination by the skin and were not due to surface contamination.

Under certain conditions of climate the amount of lead eliminated in the sweat may greatly exceed that excreted in the urine.

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ERYTHRÆMIC MYELOSIS AND MYELOID LEUCHÆMIA[1]

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THE fact that a definite relationship exists between chronic myeloid leuchæmia and *polycythæmia vera* has been known for many years, and recently these diseases together with myelosclerosis and their variants and transitional stages with many synonyms have been classed together by Dameshek (1951) and others under the heading of "the myeloproliferative syndromes". Robson (1953) has discussed their pathogenesis.

Up to date the parallel is less evident in the more acute proliferations of the bone marrow. The rare conditions of acute erythræmic myelosis and erythroleuchænia have been described and characterized by Di Guglielmo, and a chronic type of erythræmic myelosis by Heilmeyer and Schöner (Leitner, 1949). Schwarz and Critchlow (1952) have recently reviewed the literature, and pointed out that many cases reported earlier were in fact cases of Cooley's anæmia. They have set out the criteria for diagnosis, and discussed the pathogenesis of the condition.

The case to be described is of interest because, although it initially fell into the clinical picture of erythræmic myelosis, after a year the patient died with clinical and laboratory findings of myeloblastic leuchæmia. Another interesting feature was evidence of a hypersplenic effect during the initial stages of her disease, and during the terminal phase of myeloblastic leuchæmia inconclusive evidence of hæmolytic anæmia.

CASE REPORT

In December, 1952, the patient, a housewife, aged forty-six years, was first admitted to hospital. She had complained of progressive tiredness for three months, and over the previous month had received injections of liver extract and vitamin B_{12}, and had taken iron pills in large doses with no effect. The relevant past history was that one year before she had received radium treatment for a rodent ulcer on the face, and three years before she had had an attack of cystitis. Investigation of the family history revealed no significant events. Her occupation was that of cook, but five years before she had worked in a garage and used various solvents, whose exact nature was not established. She had lost 15 kilograms in weight recently, her appetite being poor, but her dietary habit was satisfactory.

[1] Received on March 22, 1954.

On her admission to hospital she was pale and obese. The spleen was palpable 6·0 centimetres below the left costal margin, and the liver was palpable 1·0 centimetre below the right costal margin. No lymph glandular enlargement was detected. A few purpuric spots were present over the right arm. The urine contained a trace of albumin and on microscopic examination an occasional erythrocyte per high-power field after centrifugation. No other physical abnormalities were detected. Over the next few weeks numerous special investigations were carried out, which are here summarized. The hæmatological data for this and subsequent admissions to hospital are shown in Table I.

The blood picture (on her admission) was as follows: the hæmoglobin value was 40% (5·9 grammes per 100 mils); the red cells numbered 2,000,000 per cubic millimetre, the nucleated cell count being 500. The differential count was as follows: 20% segmented neutrophile cells, 16% old metamyelocytes, 1% myelocytes, 1% eosinophile cells, 5% promyelocytes, 5% monocytes, 52% lymphocytes. There were 44 normoblasts per 100 leucocytes, mainly late polychromatic in type. The red cells showed considerable anisocytosis and were well hæmoglobinized. Reticulocytes numbered 2%. Platelets appeared scanty. The platelet count was 13,000 per cubic millimetre. Gastric analysis revealed histamine-fast achlorhydria. The sternal marrow was very cellular. The ratio of nucleated erythrocytes to leucocytes was 1·0 : 0·7; 15% of the cells were myeloblasts, 12% promyelocytes, 1·5% neutrophile myelocytes, 4% neutrophile metamyelocytes, 6·5% lymphocytes, 5·5% pronormoblasts, 13·5% basophilic normoblasts, 11% early polychromatic normoblasts, 25% late polychromatic normoblasts, 5% pyknotic normoblasts, 0·5% mitotic figures, 0·5% reticulum cells. (Although most recorded cases of erythræmic myelosis have shown numbers of "blast" cells in the marrow, they are usually referred to as reticulo-endothelial cells. Subsequent events as well as their morphology indicate that in this case they were myeloblasts. For this reason the diagnosis of erythroleuchæmia might be considered more accurate.)

X-ray examination of the chest, pelvis and skull gave normal findings. The blood urea content was 33 milligrammes *per centum*. The cephalin flocculation test gave positive result. The Wassermann and Kahn tests gave negative results. The erythrocyte sedimentation rate (Westergren) in one hour was 235 millimetres. The serum bilirubin content was three units *per centum*. Several determinations of fæcal stercobilinogen were made; in two instances the content was raised, 1,600 milligrammes *per centum* being the highest. Red cell saline fragility was normal. Cold agglutinins were absent. The Coombs test gave a negative result. Tests for hæmagglutinins and hæmolysins with trypsinized cells at various temperatures gave negative results. In the adrenaline test (Wintrobe) the white cell count rose from 1000 to a maximum of 1700 per cubic millimetre.

TABLE I

Main Features of Peripheral Blood Examinations

Date	Transfusions (Pints)	Hæmoglobin Value (Percentage)[1]	Nucleated Cells per Cubic Millimetre	Leucocytes per Cubic Millimetre	Normoblasts per Cubic Millimetre	Myeloblasts per Cubic Millimetre
31.12.52	—	46	500	350	150	Nil
2. 1.53	2	—	—	—	—	—
15. 1.53	3	—	—	—	—	—
19. 1.53	2	70	1,100	705	395	22
23. 1.53	—	83	900	880	20	Nil
2. 2.53	—	55	2,000	1,960	40	Nil
10. 2.53	4	40	700	490	210	Nil
12. 2.53	—	70	900	850	50	8
16. 2.53	—	67	1,400	1,370	30	13
24. 2.53	—	43	1,100	830	270	24
25. 2.53	7	—	—	—	—	—
25. 2.53			Splenectomy			
27. 2.53	—	89	20,000	5,000	15,000	Nil
5. 3.53	—	86	1,000	990	10	10
15. 5.53	—	57	20,000	2,800	17,200	14
27. 5.53	—	66	25,000	1,120	23,880	Nil
1. 6.53	2	—	—	—	—	—
11. 8.53	2·5	—	—	—	—	—
4. 9.53	—	56	100,000	9,500	90,500	5,000
6. 9.53	3	—	—	—	—	—
29. 9.53	2	—	—	—	—	—
10.10.53	2	—	—	—	—	—
3.11.53	3	—	—	—	—	—
6.11.53	2	—	—	—	—	—
11.11.53	—	78	140,000	136,600	3,400	130,400
17.11.53	—	55	180,000	176,600	3,400	161,500

[1] 14·8 grammes *per centum* = 100%.

The course during this stay in hospital was marked by a steadily falling hæmoglobin value, for which the patient was given blood transfusions during the ten weeks while she was in hospital, 18 pints of blood being given. During the first two weeks she ran a "swinging" temperature to 104° F. associated with an inflamed throat, for which she received penicillin and later streptomycin. She was also given a course of folic acid. As well as the occasional crops of petechiæ, other manifestations of the thrombocytopenia were severe epistaxis and retinal hæmorrhages. She also developed thrombophlebitis in one leg. Although a diagnosis of erythræmic myelosis was made at this stage, because of the poor outlook and biochemical evidence suggesting hæmolysis, together with a fall in hæmoglobin value in excess of that to be expected from simple arrest of red cell production, splenectomy was decided on. This was carried out eight weeks after her admission to hospital, a course of cortisone and penicillin being given before operation. After splenectomy, the results of blood examination were as follows: the hæmoglobin value was 89% (13·1 grammes *per centum*); the red blood cells numbered 4,000,000 per cubic millimetre; nucleated cells numbered 20,000 per cubic millimetre. The differential count (including normoblasts) was as follows: segmented neutrophile cells 9%, old metamyelocytes 12%, eosinophile cells 0·5%, monocytes 0·5%, lymphocytes 2·5%, normoblasts 75%. The normoblasts were mainly late polychromatic or pyknotic with a few basophilic normoblasts. The platelet count had risen to 48,000 per cubic millimetre, but within two weeks of splenectomy the platelet count had fallen to the original level, and the total, nucleated cell count was 1000 per cubic millimetre only a very occasional normoblast being present. An occasional Howell-Jolly body was seen in this and subsequent films.

Macroscopically the spleen, which weighed 700 grammes, was firm and deep red in colour, with prominent Malpighian bodies. Microscopically the pulp was congested, and contained a number of normoblasts and quite numerous megakaryocytes. The follicles were prominent, containing well marked germinal centres. It was apparent that the patient was maintaining her hæmoglobin level after the operation, and she was discharged from hospital.

In May, 1953, the patient was readmitted to hospital for blood transfusion. She had been suffering from menorrhagia. On this examination the blood picture was as follows: The hæmoglobin value was 57% (8·5 grammes *per centum*), the red blood cells numbered 2,500,000 per cubic millimetre, and the nucleated cells 20,000 per cubic millimetre. The differential count (including normoblasts) showed that 1·5% were segmented neutrophile cells, 1% old metamyelocytes, 0·5% myeloblasts, 11% lymphocytes and 86% normoblasts. She was next readmitted to hospital in September, 1953, having meanwhile attended another hospital and received a transfusion of two pints of blood. Again her main trouble was severe menorrhagia, and it was therefore decided to induce an artificial menopause by a uterine radon seed implant. At this time blood examination gave the following information: the hæmoglobin value was 56% (8·2 grammes *per centum*, the red blood cells numbered 2,800,000 per cubic millimetre and nucleated cells numbered 100,000 per cubic millimetre. The differential count (including normoblasts) was as follows: segmented neutrophile cells 1·5%, myelocytes 0·25%, promyelocytes 0·25%, myeloblasts 5%, lymphocytes 2%, mitotic figures 0·5%, normoblasts 90·5%. The normoblasts were mainly late polychromatic in type.

Iliac crest biopsy at this time revealed a cellular marrow. The myelogram gave the following information: myeloblasts 17%, promyelocytes 2%, neutrophile myelocytes 0·5%, eosinophile myelocytes 1%, lymphocytes 3·5%, pronormoblasts 0·5%, basophile normoblasts 1·5%, early polychromatic normoblasts 8·5%, late polychromatic normoblasts 55·5%, pyknotic normoblasts 6%, basophilic megaloblasts 1%, mitotic figures 2%. The ratio of nucleated erythrocytes to

leucocytes was 1 : 0·3. A very occasional megakaryocyte was seen. It had been noted previously that the nuclear structure of some of the normoblasts was bizarre; but now that the normoblasts had reached their highest level in the peripheral blood this finding was very pronounced. The nuclei showed very coarse hyperchromatic clumping of chromatin. Irregular lobulation, sometimes with several distinct small lobes, was pronounced. A few normoblasts were multinucleate. Mitoses of normoblasts showed irregular bizarre patterns.

The platelet count was 26,000 per cubic millimetre. The bleeding time (Duke) and clotting time (Lee and White) were normal, as was clot retraction. The Coombs test now produced a positive reaction on two occasions, but no cold agglutinins, autoagglutinins or isoagglutinins were detected by the use of trypsinized cells at various temperatures, nor were warm hæmolysins detected. The serum bilirubin content was two units. The total serum protein content was 6·7 milligrammes per 100 millilitres; the albumin and globulin contents were respectively 4·3 and 2·4 milligrammes per 100 millilitres. The erythrocyte sedimentation rate (Westergren) in one hour was 48 millimetres. The fæcal stercobilinogen content was 100 milligrammes per 100 millilitres. No methæmalbumin was detected in blood, or hæmosiderin in urine. The patient was given a transfusion of six pints of blood during this period. During this time in hospital she had also suffered a mild attack of pyelocystitis due to *Bacterium coli*.

She was admitted to hospital in November, 1953, for the last time, complaining of a sore throat, which had been treated by her local doctor for several days with penicillin and sulphonamide drugs. She complained of severe dysphagia and vomiting. The tonsils were grossly enlarged but not acutely inflamed, and a few small glands along the jugular chain were palpable each side of the neck. Culture of material from the throat revealed the presence of *Streptococcus viridans*, *Staphylococcus aureus* and *B. coli*. The peripheral blood picture after a transfusion of two pints of blood was as follows: the hæmoglobin value was 78% (11·5 grammes *per centum*), the red blood cells numbered 3,200,000 per cubic millimetre, and the leucocytes numbered 140,000 per cubic millimetre. The differential leucocyte count was as follows: neutrophile cells 2·5%, myeloblasts 95·5%, lymphocytes 2%, normoblasts 2·5 per 100 leucocytes. Within a few days her tonsils were acutely inflamed and she developed severe and intractable diarrhœa. No pathogenic organisms were isolated from the fæces. She had a persistently high "swinging" temperature, with peaks to 104° F. Aminopterin was given, two milligrammes at once and one milligramme daily. This had no effect upon the blood picture, and six days later the hæmoglobin value was 55% (8·1 grammes *per centum*), the erythrocytes numbered 3,600,000 per cubic millimetre, and the leucocytes numbered 180,000 per cubic millimetre, 94% being blast cells of myeloid type, and two normoblasts being present per 100 leucocytes. A few of the blast cells gave a weakly positive peroxidase reaction. During this period in hospital she received five pints of blood. She died three weeks after her admission.

The Post-Mortem Examination

The following were the findings on macroscopic examination:

There was bilateral pulmonary œdema. The tonsils were very enlarged, being composed of soft grey tissue with an ulcerated surface, and several soft, enlarged lymph nodes were present on both sides of the neck. There was slight swelling of the mucosa of the ileum, while most of the mucosa of the large bowel was shaggy and necrotic and the wall thickened. The liver was very large, soft and pale. A small splenicule was present. The kidneys were enlarged, and on section pale. The mucosa of the uterus was necrotic. Abdominal lymph nodes were slightly enlarged. The marrow of the thoracic and lumbar vertebræ and the femur was soft and grey.

Microscopic examination revealed infiltration with myeloblasts in pulmonary alveoli, lymph nodes, uterus, thyroid, large bowel, liver and kidney. In the sections of lumbar vertebræ the marrow was replaced by sheets of myeloblasts, many mitotic figures being present. However, scattered normoblasts were also present.

DISCUSSION

Although it is obvious that hæmolysis was not the primary cause of the patient's marrow hyperplasia, it is interesting that during the first few weeks after her admission to hospital the findings suggested abnormal blood destruction, and that after splenectomy she required far less frequent transfusion. Again, during the last two months the fact that the Coombs test result was positive suggests that hæmolysis played a part in her anæmia, although this was not confirmed by other tests performed at that time, and because of her severe menorrhagia this was difficult to assess.

The presence of a hæmolytic anæmia with a positive response to the Coombs test is a not infrequent occurrence in lymphatic leuchæmia (Fisher and others, 1952) but rare in myeloid leuchæmia (Jonsson and others, 1950). It is worthy of note that Schwartz and Critchlow (1952), in discussing their own cases and the pathogenesis of this condition of erythræmic myelosis, considered that an additional hæmolytic mechanism in the anæmia of the condition was not at all unlikely to be found ultimately.

With regard to the place of splenectomy in erythræmic myelosis, it cannot influence the ultimate course of the disease, but when the evidence suggests that hypersplenism is present it may be a worthwhile symptomatic form of treatment which may render existence more comfortable and perhaps prolong life.

A similar case has been reported recently by Verloop and others (1952); they give the history of a man, aged twenty-nine years, whose clinical and laboratory findings ran very closely parallel to this case, the patient dying eleven months after being first examined. Discombe and Nickol (1953), in a report of a case with similar features, make the following statement:

It is suggested that acute granulocytic leuchæmia sometimes has an erythroblastic onset and that it may be impossible to differentiate between erythræmic myelosis (should such an entity exist) and acute

leuchæmia with an erythroblastic onset. Since nothing is known of the pathogenesis of these diseases it may be desirable to group them together instead of subdividing them.

Verloop and others point out that because of the use of blood transfusion and antibiotics, patients who in the past would have died while still in the stage of erythræmic myelosis will now be expected to show this leuchæmic termination.

CONCLUSION

It is thought that erythræmic myelosis may come to be regarded as a phase of an acute myeloproliferative disorder which, provided that the patient can be kept alive, will often terminate with a frankly leuchæmic picture. One advantage of using a generic title such as "chronic and acute myeloproliferative disorders" is that as the clinical state of the patient progresses in a phasic fashion, the alterations in diagnoses that occur do not appear as contradictory events, but appear as episodes in the natural course of a disease.

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FLUID RETENTION DURING METHONIUM THERAPY[1]

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The use of methonium derivatives in the treatment of hypertension is commonly accompanied by side effects, which can generally be attributed to the cerebral effects of excessive hypotension, or to interruption of the activities of the autonomic nervous system by ganglionic blockade. In this paper are described changes in fluid balance observed during treatment of hypertension with methonium drugs, the immediate cause of which is not clear.

Subjects and Methods

The 17 patients studied were selected from a series of 50 patients who were admitted to hospital for treatment of severe hypertension. Most of the patients were excluded from this study for the following reasons: weight records were not kept or were inadequate, methonium therapy was discontinuous, or there were unrelated complications. On the other hand, some patients were deliberately included because they had severe renal impairment. Our study of these records has been in large part retrospective. Ten of the 17 patients presented the ocular changes of malignant hypertension (papillœdema, retinal hæmorrhages and exudate).

Initially, the patients were confined to bed, or permitted limited activity according to their clinical state. A period up to two weeks was spent in recording blood pressures, in giving single test doses of methonium drugs, "Seconal" and "Regitine", and in assessment of cardiac and renal state. The blood urea content was estimated with the patient fasting overnight. After the ingestion of 15 grammes of urea, the urine was collected hourly, the blood urea content was estimated, and the following values were calculated: urea clearance (by the method of Fowweather), the amount of urea excreted in three hours, and the concentration of urea in the hourly specimens of urine. After these initial observations, treatment with methonium was commenced, the dose being adjusted to produce an optimal fall in blood pressure. The treatment adopted in the majority of cases comprised subcutaneous injections of hexamethonium bromide[2] or pentapyrrolidinium bitartrate,[3] given every eight hours.

Throughout the stay in hospital, fluid balance was studied by daily record of fluid intake, output, and weight, as described by Lowe (1951).

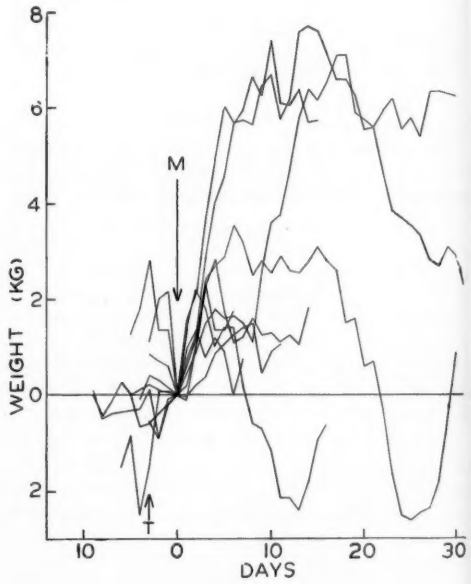

Figure I

Superimposed weight curves of nine patients showing fluid retention. M indicates commencement of continual methonium therapy; T indicates a single test injection of methonium in the patient whose weight curve is adjacent (see also Figure II)

Observations

In eight patients there was no disturbance of fluid balance related to the administration of methonium. Four of these were in the

[1] Presented at the Annual Meeting of the Australasian Cardiac Society, May, 1954.

[2] "Vegolysen", May and Baker.
[3] "Ansolysen", May and Baker.

malignant phase. Two patients who presented with congestive cardiac failure lost the excess fluid at a rate uninfluenced by methonium.

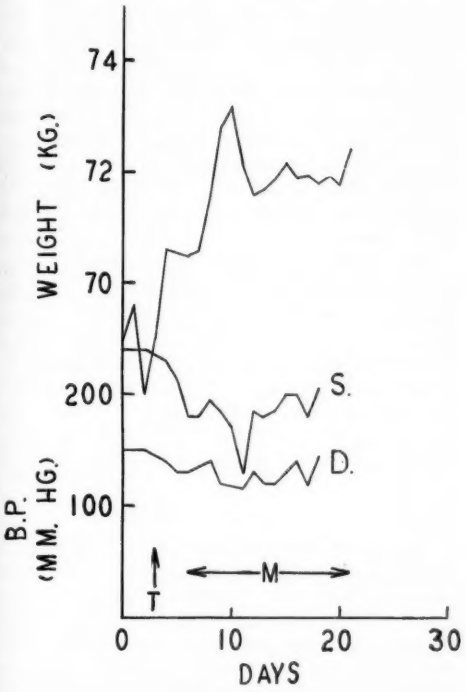

FIGURE II

Example of weight change associated with methonium therapy. Blood pressure records were taken with the patient lying flat. T, single test injection of methonium; M, continual methonium therapy; S, systolic blood pressure; D, diastolic blood pressure

Nine patients showed evidence of fluid retention clearly related to the institution of regularly repeated doses of methonium (Figure I). Six of these were in the malignant phase. In a few cases these changes occurred with a single injection of methonium, but the retained fluid was promptly excreted in the next twenty-four hours in all but one case (Figures I and II). Fluid retention was usually not pronounced until treatment was given continuously.

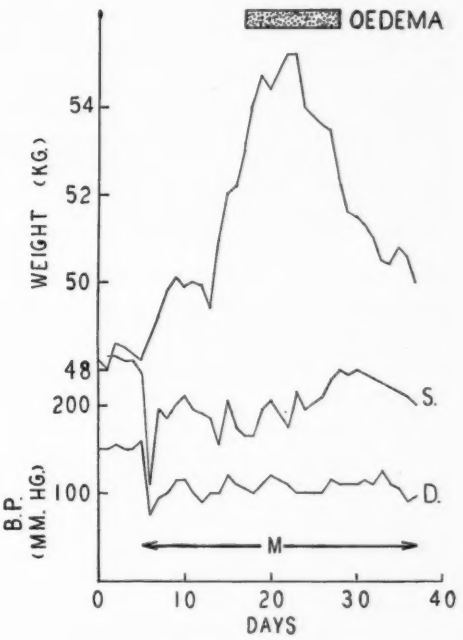

FIGURE III

Example of weight change associated with methonium therapy. Œdema occurred, and disappeared without diuretic therapy. M, continual methonium therapy; S, systolic blood pressure; D, diastolic blood pressure

The maximum increase in weight of each patient is shown in Table I. In most, the degree

TABLE I

Change in Weight, Clinical Signs and Course in Patients Exhibiting Fluid Retention During Methonium Therapy

Patient Number	Greatest Rise in Weight During Methonium Therapy (Kilograms)	Clinical Signs of Fluid Retention Appearing During Methonium Therapy	Treatment for Fluid Retention	Subsequent Change in Weight
I	2·3 (2·9%)	Nil	Nil	Maintained
II	1·5 (2·0%)	Nil	Nil	Maintained
III	1·4 (2·0%)	Nil	Nil	Fell to normal
IV	7·0 (14·4%)	Peripheral œdema	Nil	Marked spontaneous drop
V	7·4 (11·7%)	Peripheral œdema	Nil	Fell slightly
VI	2·2 (3·8%)	Nil	Nil	Fell below initial level, then rose slightly
VII	3·6 (5·3%)	Peripheral œdema, increased venous pressure, pulmonary congestion	Mersalyl injections	Fell below initial level, then rose again
VIII	7·7 (12·2%)	Peripheral œdema	Mersalyl injections	Fell slightly
IX	4·3 (6·3%)	Nil	Nil	Fell to moderate extent

of fluid retention was not serious; part of the retained fluid was usually excreted in a few days, though in others there was persistent retention of fluid during the period in hospital. No steps were taken to treat this in the absence of clinical signs.

Four patients developed peripheral œdema during methonium treatment. In one, this was accompanied by pulmonary œdema, and by a considerable rise in jugular venous pressure. These signs were relieved by injections of mersalyl, without cessation of methonium treatment. This patient has remained œdema-free as an out-patient, with full physical activity and excellent reduction of blood pressuer. Another patient lost œdema and part of the retained fluid after injections of mersalyl.

Table II

Patients having Methonium Therapy. Daily Intake of Fluid Related to the Sensation of Dryness of the Mouth

Patient Number	Without Dryness of Mouth		With Dryness of Mouth	
	Average Daily Intake (Millilitres)	Days Observed	Average Daily Intake (Millilitres)	Days Observed
I	1425	8	1100	9
II	1600	7	1630	13
III	2100	4	2400	4
IV	3440	6	3225	6
V	3180	8	3210	8
VI	1850	12	1950	4
Mean ..	2266	—	2250	—

The other two patients lost œdema and most of the retained fluid spontaneously. In one of these there was a gradual rise in blood pressure despite methonium therapy (Figure III); in the other, reduction of blood pressure was maintained.

Most patients frequently complained of intense dryness of the mouth during methonium therapy. We noted that this was not usually accompanied by a rise in fluid intake. In six cases, the presence or absence of this symptom was noted daily, and compared with fluid intake (Table II).

Dryness of the mouth in patients treated with methonium drugs is presumably due to interruption of the secretomotor nerves to the salivary glands. Although thirst is often associated with the sensation of dryness of the mouth, these observations afford clinical support for the view that dryness of the mouth is not *per se* the immediate cause of the sensation of thirst.

Discussion

We have been unable to establish clearly any difference between the two groups in respect of the fall in blood pressure or the degree of renal impairment as shown by the methods described. These observations have been made incidentally in the course of a therapeutic study of methonium drugs, in which the methods of treatment and of assessing blood pressure control have been changed. However, we think that the phenomenon of fluid retention is more likely to occur in those patients with severe renal disease or a pronounced fall in blood pressure.

The effects of single doses of methonium drugs on renal function have been recorded by numerous workers. It is generally agreed that glomerular filtration is reduced, though changes in other aspects of renal hæmodynamics have been variable. McQueen and Trewin (1952*a*) stressed the reduction in urine flow, and found that this persisted although glomerular filtration tended to return towards its previous level. They observed also a comparable fall in sodium excretion.

The possibility of increasing renal impairment has been stressed in clinical trials. However, Smirk and Alstad (1951) found neither rise in blood non-protein nitrogen level nor clinical indication of further renal impairment after effective blood pressure reduction in four patients with renal insufficiency. Campbell *et alii* (1952) included in their series five patients with chronic nephritis, and stated that poor renal function was not a contraindication to treatment. Two of these patients died during treatment—one with cardiac failure, the other with uræmia. McQueen and Trewin (1952*b*) have described the treatment of 45 patients, of whom half had primary renal disease, but did not record fluid retention as a complication. Palmer (1952) suspended the treatment of two of her patients after a rise in blood urea level had occurred; in another, the blood urea level rose initially, then fell despite continued treatment.

Ford *et alii* (1953) have studied renal function after continuous treatment with hexamethonium for one month. They found that glomerular filtration rate, renal plasma flow and TmPAH fell during ambulation to a greater extent and to a lower value than before treatment, and that urine flow and sodium and potassium excretion were likewise reduced to a greater degree; but despite this none of their patients showed signs of œdema, or gain in weight.

They showed that the reduction of renal activities observed during ambulation appeared to be compensated by an increase during a subsequent period of recumbency.

We cannot say whether the changes we have observed are common. Although the studies cited included patients with comparable hypertensive disease, the techniques of treatment have probably differed in several regards. The majority of our patients did not show clinical signs of fluid retention. In those who ultimately developed œdema, this did not appear for some days after the institution of methonium therapy, although fluid retention commenced immediately. Without the fluid balance charts, we should probably have overlooked the relationship and attributed the fluid retention to hypertensive disease.

The spontaneous return toward normal fluid balance noted in some of our patients was not consistently associated with a rise in blood pressure. In these cases there may have been either a rise in glomerular filtration rate despite maintenance of lowered blood pressure, or renal tubular adaptation to lowered glomerular filtration, as described by Platt (1952).

Practical Applications

It is generally agreed that treatment of hypertension with methonium drugs is not contraindicated in patients with impaired renal function. However, in addition to the more obvious complications of oliguria and uræmia, fluid retention should be anticipated. This is best detected by accurate daily weighing. Gradual lowering of blood pressure is desirable to avoid both complications. If fluid retention occurs, the dose of methonium should be reduced temporarily, bed rest enforced, and restriction of salt intake and the exhibition of diuretics instituted as required. Effective methonium therapy may still be attained in these cases, although stabilization may require several weeks longer.

SUMMARY

The occurrence of fluid retention in hypertensive patients treated with methonium drugs is described, and the relation of this phenomenon to methonium therapy discussed. It is concluded that methonium therapy may under certain circumstances precipitate fluid retention. Although the mechanisms of this complication have not been demonstrated, it is thought that a combination of rapid reduction in blood pressure and renal impairment is a predisposing factor to this condition, and methods for its prevention or treatment are described.

Further evidence is provided that dryness of the mouth is not the immediate cause of thirst.

ACKNOWLEDGEMENTS

We are indebted to Dr. A. J. Barnett for his cooperation and advice during this study, which was made upon patients in his care, and to the medical and nursing staffs of the Clinical Research Unit for their help in collecting the observations.

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ANNUAL MEETING, 1954

The Annual Meeting of the College in 1954 was held at Melbourne from May 26 to 29. It was attended by 118 Fellows and 98 Members representative of all the Australian States and of New Zealand. The President, Dr. C. G. McDonald, was in the chair.

Scientific Sessions

Two scientific sessions were held in the Lecture Hall of the Royal Australasian College of Surgeons. The following contributions were given: "The Immediate and Remote Results obtained by Pulmonary Valvotomy in Pulmonary Stenosis", by E. J. Halliday; "The Place of Lumbar Sympathectomy in the Treatment of Occlusive Arterial Disease of the Legs", by A. J. Barnett; "Pneumonia", by H. K. Lefroy; "Renal Biopsy in Diabetes Mellitus", by H. P. Taft; "Symptoms and their Significance", by A. J. M. Sinclair; "Beriberi Heart Disease", by R. B. Blacket and Jean Palmer; "Fundamental Aspects of Allergy", by E. R. Trethewie; "Hæmophilia: A Syndrome under Review", by Ronald Sawers.

An abstract has been received of the paper "Symptoms and their Significance", presented by A. J. M. Sinclair, as follows:

> Difficulties arise in the assessment of symptoms due to the limitation in the meaning of words which have a special significance as a vehicle of meaning for each individual. The method of presentation of symptoms of physical illness is peculiar to each patient and is coloured by emotional states such as anxiety, dependency, resentment or hostility. The anxious person betrays his anxiety by hand movements, by mannerisms of alertness and other indicators. It is common for him to express his real anxieties either at the beginning or at the end of an interview. His efforts at concealing his tension may in themselves be evidence of underlying anxieties. The dependent person often appears to be co-operative and may be a "nice" patient because of his dependence on the physician and readiness to accept the pronouncements of his medical adviser. Further and more frequent medical attention becomes necessary as the patient becomes more dependent. The hypochondriacal patient often gives the impression that he is presenting evidence rather than symptoms and that he suffers more from the need to be believed than from the symptoms themselves. The patient who has in addition to his physical illness considerable repressed or unrepressed aggression finds it difficult to relate himself to his physician. He tends to emphasize the limitations which illness puts upon him and often attributes illness to a crushing unique stress beyond his control. He gives ample evidence that he regards the illness as an unjust imposition. Such a person reacts poorly to implied or open criticism during the medical interview. He is often unable to "take" drugs or follow a medical régime. The patients with an hysterical personality may use physical symptoms in the same way as other hysterical patients use paralysis and allied somatic dissociations. A typical characteristic of this symptom presentation is that the patient exhibits a shallow and inappropriate emotional reaction during the recital of symptoms. There are many techniques in symptom presentation in the hysterical person, but the characteristic of all of them is the attitude of not being responsible for the illness. The symptoms are presented to the physician with the implied request that he remove them. The patient does not appear to participate in the illness. It may be of value that during history taking, notes should record the patient's behaviour, minor emotional responses, and his particular technique of symptom presentation in addition to the routine chronological account of his illness.

Clinical Meetings

Clinical meetings were held at St. Vincent's Hospital and at the Royal Melbourne Hospital. The following demonstrations were given: "Clinical and Metabolic Studies on Two Patients with Hyperchloræmic Renal Acidosis and Osteomalacia", D. G. Duffy and B. Hudson; "Gastrointestinal Polyposis", L. Murphy; "Adrenal and Thyroid Insufficiency Presenting in Coma", W. Hamilton Smith; "Patent Ductus Arteriosus with Gross Cardiac Embarrassment in Early Infancy", M. L. Powell; "Hyperlipæmia", R. A. Joske (Clinical Research Unit, Royal Melbourne Hospital); "Tuberculous Meningitis Treated with Cortisone" and "Disseminated Lupus Erythematosus Treated with Cortisone", G. A. Penington's Unit; "Coarctation of the Aorta in Middle Age", Allan Wynn; "Pulmonary Sarcoidosis Treated with Cortisone", J. E. Clarke; "Unilateral Pyelonephritis and Hypertension", W. McI. Rose.

College Ceremony

The Annual Ceremony of the College was held in the Malvern Town Hall, Malvern, Victoria. An audience of 600 was present. The President, Dr. C. G. McDonald, welcomed the Governor of Victoria and Lady Brooks, the Chief Justice of the High Court of Australia, Sir Owen Dixon, and Lady Dixon, the Lord Mayor of Melbourne and other distinguished guests. He said that it was customary for the College to hold at least once each year a public ceremony, at which the public might glean something of the purposes of its existence as a Royal College. Physicians were not philosophers standing on an intellectual eminence and musing on the world of men and women who passed in pageantry before them. Like other professional

men—the lawyer, the engineer, the architect—they were part of the pageant itself, lending colour to the kaleidoscope of human activity. In greater degree than other professional men they were the slaves of progress and the ever-restless spirit of the age in that they had to keep abreast of the technical advances of their craft, and if they failed their patients with *The Reader's Digest* in hand would soon put them wise.

It had been truly said that in all education there was, first, the teaching of technique and second, the sharing in tradition. Of the two tradition was the more important because it was part of the spiritual inheritance of the race. It was the tradition of medicine—its history stretching back to the remote past, the learning of its teachers handed on from generation to generation down the ages, and above all its lofty standards of conduct first enunciated by a great Greek physician on the island of Cos—that made doctors worthy to rank with members of other great professions. The Royal College of Physicians of London, founded by Linacre under a charter granted by Henry VIII four hundred years earlier, was the exemplar and pattern for the formation of The Royal Australasian College of Physicians. Beside her the new College seemed young indeed, for she was scarce sixteen years old. But equally with her the Australasian College was proud of the record of medicine, of the great men of all countries who had shed lustre on its art, and of its great prophets from Hippocrates to Osler.

Physicians achieved their greatest triumphs, not by prodigies of diagnosis or by the use of the latest antibiotic, but by the comfort they brought to their patients in the consulting-room or by the bedside; not so much by their science as by their art; and never so much as when their every action and every word were inspired by that ineffable charity that marked the great. In the present dark and difficult days, when the spirit of man had been crushed by two disastrous wars and when the optimism of their fathers, voiced by Browning and other prophets of the nineteenth century, had been rudely shaken, physicians should come to their small but important tasks with hearts that beat warmly for those whom they served. In reconstructing man's body they would then help much in the repair of his wounded and dejected spirit.

His Excellency the Governor of Victoria, Sir Dallas Brooks, welcomed to the State of Victoria those Fellows and Members of the College who had come from New Zealand and from the other States of the Commonwealth. He was appreciative of the fact that physicians were making for the good of mankind. Science had done extraordinary things for the world. However, he could not help remembering one criticism which he had made to the Australasian Medical Congress (British Medical Association) which had been held in Melbourne in August, 1952, that the medical profession had so far failed to find a cure for the universal scourge known as the common cold. He asked the physicians what they proposed to do about it. His Excellency then called attention to the great value of the family doctor in the social economy. The family doctor was the advance-guard and the backbone of the profession. By his knowledge, his efficiency and his humanity he won the confidence of his patients. Finally, His Excellency made mention of the part which physicians could play in the imminent problems of South-East Asia. He called attention to the danger from the north, and showed that there was a ripe field for the harvesting if the medical profession would help the development of the peoples of South-East Asia by an extension of its interest in the Colombo Plan.

The President introduced to the audience Professor A. D. Trendall, Master of University House, Canberra, who had honoured the College by accepting an invitation to deliver the Arthur E. Mills Memorial Oration. Professor Trendall then delivered the Oration, which was entitled "The Medicine Man and the Medical Man". (See *The Medical Journal of Australia*, 1954, 2: 117.)

Guests were entertained at supper at the conclusion of the Ceremony.

OFFICE-BEARERS

The following is the constitution of the Council for the period 1954–1956.

President: C. G. McDonald.

Vice-Presidents: Ralph Whishaw, A. D. S. Whyte (New Zealand), Ian J. Wood.

Censor-in-Chief: T. M. Greenaway.

Honorary Treasurer: W. P. MacCallum.

Honorary Secretary: H. Maynard Rennie.

Elected Councillors: Fellows: Sir Charles Blackburn, Clive Fitts, T. M. Greenaway, J. G. Hayden, A. Holmes à Court, F. Ray Hone, Bruce Hunt, J. A. D. Iverach, Guy Lendon, K. B. Noad, E. G. Sayers, S. A. Smith, Allan S. Walker and Ian J. Wood; Members: J. J. Billings and D. S. Stuckey.

Executive Committee, 1954–1956: C. G. McDonald (President), W. P. MacCallum (Honorary Treasurer), H. Maynard Rennie (Honorary Secretary), T. M. Greenaway, A. Holmes à Court, Sir Alexander Murphy, Ian Wood and S. A. Smith.

Boards of Censors

Censor-in-Chief: T. M. Greenaway.

Australian Board: Eric Clarke, Clive Fitts, J. L. Frew, Ray Hone, A. W. Morrow and K. B. Noad.

New Zealand Board: Professor F. H. Smirk (Senior Censor for the Dominion), I. McD. Allen, C. R. Burns, J. F. Landreth, S. L. Ludbrook and J. M. Twhigg.

EDITORIAL COMMITTEE OF "AUSTRALASIAN ANNALS OF MEDICINE"

The Editorial Committee of AUSTRALASIAN ANNALS OF MEDICINE was reappointed for the period 1954–1956. It is now constituted as follows: A. Holmes à Court (Chairman), Mervyn Archdall (Editor), Professor E. Ford, C. R. B. Blackburn, Ralph Reader (Honorary Secretary) and B. C. Sinclair-Smith (Assistant Honorary Secretary).

The editorial representatives are as follows: E. G. Sayers, J. O. Mercer, M. K. Gray and Professor F. H. Smirk, of New Zealand; Sir Alexander Murphy and Ian Mackerras, of Queensland; T. E. Lowe, Ian Wood and A. J. M. Sinclair, of Victoria; Professor A. A. Abbie and E. B. Sims, of South Australia; Cyril Fortune and Eric Saint, of Western Australia; J. L. Grove and Ralph Whishaw, of Tasmania.

MEMBERSHIP

Admission of Honorary Fellows. At its Meeting on May 26, 1954, Council admitted *in absentia* to Honorary Fellowship William Bosworth Castle, of Boston, Massachusetts, United States of America, and Robert Frederick Loeb, of New York, New York, United States of America, in recognition of the services rendered by each to the science and practice of medicine and of the courteous and helpful reception afforded by them to physicians from Australia and New Zealand visiting the United States of America.

Admission of Fellows. The following Fellows were admitted after election at the meeting of the General Body of Fellows on May 26, 1954: under Article 44: Professor H. N. Robson, of South Australia; under Article 42: M. H. Aiken and C. G. Riley, of New Zealand; Leslie P. Bidstrup, of the United Kingdom; C. R. Furner, S. J. M. Goulston, K. S. Harrison, Mary J. Heseltine, James Isbister, M. R. Joseph, F. R. Magarey, V. J. McGovern, S. R. Reader and S. E. L. Stening, of New South Wales; D. G. Duffy, H. B. Kay, P. J. Parsons, W. McI. Rose, H. J. Stephens and Marion B. Wanliss, of Victoria; J. M. Bonnin and R. F. West, of South Australia.

Admission of Members. The following candidates, who were successful at an examination held in Auckland, New Zealand, in February, 1954, were admitted to Membership on May 26, 1954: R. H. Caughey, H. K. Ibbertson, J. K. Laing, T. V. O'Donnell and I. A. Prior. The following candidates, who were successful at an examination held in Australia in April-May, 1954, were admitted to Membership on May 26, 1954: C. R. Boughton, V. G. Bristow, K. G. Chatfield, A. K. Cohen, H. R. Elphick, A. G. Fisher, J. R. Kelly, W. R. Kingston, B. L. Marks, G. H. Neilson, J. C. Quoyle, M. J. Robinson, J. J. Sullivan and O. B. Tofler. Two Members were admitted under the provisions of Article 37. They are S. G. Anderson and R. Motteram, of Victoria.

Honours. Honours have been bestowed by Her Majesty the Queen upon the following Fellows of the College: Sir Alexander Murphy, Knight Bachelor; Sir Harry Wunderly, Knight Bachelor; R. S. Steel, Officer of the Order of the British Empire.

Obituary. The Council records with regret the death of N. C. Cunningham and Edgar Stephen, of Sydney, Hilda Gardner, C. V. Mackay and Douglas J. Thomas, of Melbourne, and H. S. Lucraft, of Perth, who were Fellows of the College, and of T. S. Garnet Leary, of Melbourne, and Addie Walker, of Sydney, who were Members of the College.

Membership Roll. The College now has a roll of 318 Fellows and 403 Members.

GENERAL

Sims Commonwealth Travelling Professors, 1955. Two Sims Commonwealth Travelling Professors have been appointed for 1955. They are R. I. Harris, M.C., F.R.C.S., Hon.F.R.C.S. (England), of Toronto, Canada, and Donald Hunter, M.D., F.R.C.P., of England. Dr. Harris will visit the United Kingdom, Australia and New Zealand, and Dr. Hunter will visit Canada and Rhodesia.

Curator of Historical Library. Professor Edward Ford has been appointed Curator of the Historical Library of the College.

Representative of the College. The Council appointed L. E. Hurley as the representative of the College on the Medical and Scientific Committee of the Anti-Cancer Council of Victoria.

Future Meetings of the College. The ordinary meeting in 1954 will be held in Sydney, from October 13 to 16. In 1955 the annual meeting will be held in Sydney. No ordinary meeting will be held in that year.

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